Pulmon

The Journal of Respiratory Sciences

Vol 15, Number 2 (May –Aug) 2013
ISSN 0973 – 3809

OFFICIAL PUBLICATION OF ACADEMY OF PULMONARY AND CRITICAL CARE MEDICINE

Pulmon
The Journal of Respiratory Sciences

Vol 15, Number 2 (May– Aug) 2013 ISSN 0973 – 3809

Contents

Pulmon 2013; 15:2 : 37-76

Pulmon

The Journal of Respiratory Sciences

Proprietor

Academy of Pulmonary and Critical Care Medicine

Head office (Ernakulam)

Publication data

3 issues published in a year

Journal office & Correspondence

Editor-in-chief PULMON
Dr. Suraj K.P.
Additional Professor,
Dept. of Pulmonary Medicine
Govt. Medical College,
Kozhikode, Kerala, India - 673008
E mail: drsurajkp@yahoo.com

Advertising and tariff requests

Head Office of Academy of Pulmonary and Critical Care Medicine

Dr. Kurian Oommen

Thottathil

Kavumbhagom PO

Thiruvalla -689102

Ph: 0469 2604796, 9847248015

drkurianoommen@gmail.com

Subscription rates

Personal
Single : Rs. 100
Annual : Rs. 250

Institutional
Single : Rs. 125
Annual : Rs. 300

Contact e-mail ID : drsurajkp@yahoo.com

Instructions for Authors

Instructions for submission of manuscripts are published in the journal. Also available in editorial office

Registration

Registrar of Newspapers of India
RK Puram, New Delhi
Regn. No. M6/6468/2001
ISSN 0973 – 3809

Type setting and Printing

Royal Graphics, Ph: 9847506050
Kamala Offset, Calicut
Ph: 2721020

Pulmon The Journal of Respiratory Sciences

"Committed to the Care of Lungs"

The Official Publication of the
Academy of Pulmonary and Critical Care Medicine

Academy of Pulmonary & Critical Care Medicine

Pulmon
The Journal of Respiratory Sciences

Editorial

Infection control in Tuberculosis-High time to implement the basics

Vishnu Sharma M.
Professor and Head, Dept of Pulmonary Medicine,
A J Institute of Medical Sciences, Mangalore, Karnataka.

Correspondence : Dr. Vishnu Sharma M. ,Professor and Head, Dept of Pulmonary Medicine,
A J Institute of Medical sciences, Mangalore, Karnataka.drvishnusharmag@gmail.com

"It may seem a strange principle to enunciate as the very first requirement of a hospital that it do the sick no harm" (Florence Nightingale, Notes on Hospitals, 1863).

Tuberculosis is a major public health problem in India. The incidence of new cases of pulmonary tuberculosis was about 1.5 per 1000 population in 2000 in India[1]. The global TB scenario in 2006 showed[2] that the number of New TB cases was 9.2 million {139/100,000}, HIV co-infected cases were 0.7 million. New sputum smear positive cases were 4.1 million {62/100,000} and the prevalence of TB was 14.4 million{219/100,000}. Annually, nine million new cases of active TB were reported around the world, with about 1.7 million deaths in 2009. With an estimated annual incidence of over nine million cases, tuberculosis is believed to be responsible for more adult deaths each year than any other single infectious agent[3].

India has more TB patients than any other country and accounts for one fifth of the world's incident TB cases[4]. Every year, 2 million new cases of TB are reported in India and nearly 1 million cases are smear positive; an estimated 40% of the Indian population is latently infected with M. tuberculosis[5].

When a patient with pulmonary tuberculosis coughs, sneezes or talks, bacilli get disseminated into the environment in the form of droplet nuclei. A patient with smear positive pulmonary tuberculosis can infect 10-15 persons in a year[4]. Hence it is important to educate Pulmonary Tuberculosis patients to practice proper cough hygiene[5]. Cough hygiene is one among the five steps in "Preventing TB transmission through good patient management"[6] as recommended by WHO. An annual decline in the newly occurring TB infection to the extent of 14% could halve the problem in five years.

Control of TB in high burden countries including India relies on the detection and treatment of infectious cases, mostly by testing patients attending a health clinic with chest symptoms. World Health Organization estimates suggest that in 2006 there were 4 million individuals with undiagnosed tuberculosis.

In India RNTCP emphasizes mainly on case detection and treatment. Not much

importance is given for infection control from a source of TB. Unhealthy practice of coughing and sneezing without covering mouth and nose is a high risk behavior causing transmission of respiratory pathogens. So also coughing and spitting sputum in public places should be discouraged as it may cause transmission of TB. A patient with TB is infectious before diagnosis and at least for two weeks after initiation of Anti TB treatment. Strangely enough, no cough hygiene is taught to these patients with TB when they are initiated on treatment.

Undiagnosed TB patients are a potential source of infection. In India, where most of the public places are overcrowded,it is natural that an innocent person would get infected from a source who sadly does not practise cough etiquette. Patients with suspected TB who attend health care facilities, wait for a long time and may infect others around them. In India there is no strict implementation of guidelines by RNTCP or Government regarding prevention of TB transmission.

Mycobacterium tuberculosis is usually transmitted through air, not by surface contact. M. tuberculosis, the causative agent of TB, spreads from person to person via infected aerosols created by patients with predominant lung involvement. Mycobacterium tuberculosis is carried in airborne particles called droplet nuclei that are generated when persons with pulmonary or laryngeal TB cough, sneeze, shout, or sing[7, 8] .

Coughing causes both mucus aerosolization and droplet generation. When the layer of mucus lining the airways interact with the high-speed airflow of the expulsive phase (up to100 km/h) droplets of different sizes are formed and forced up the airway tree. The particles are approximately 1-5 μm; normal air currents can keep them airborne for prolonged periods and spread them throughout a room or building. These droplet nuclei are invisible to the naked eye. Droplet nuclei can remain airborne in room air for a long period of time, until they are removed by natural or mechanical ventilation.

For TB to spread, there must be a source (a patient who has infectious TB disease) and a susceptible host (a person to inhale droplet nuclei containing M.tuberculosis). Anyone who shares air space with a person with infectious TB disease of the lungs or larynx is at risk. Studies of TB transmission indicate that the size of the infected aerosol is critical in its ability to reach and infiltrate the lung[10].

An association between cough frequency and tuberculous aerosol production and increased transmission among household contacts has been found[11]. Retrospective study of TB contacts suggests that most transmission within households occur prior to diagnosis and initiation of treatment. Advanced cavitary disease and the presence of high numbers of M. tuberculosis in expectorated sputum is associated with transmission.[12] But it is not known how early in the course of infection that these patients pose a significant risk of infecting others.

Mycobacterium tuberculosis can be transmitted even by brief contact with an infectious case[13].Close contacts are persons who share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours) with a person with pulmonary TB disease.

Persons who use tobacco or alcohol, illegal drugs, including IV drug abuse and crack cocaine are also at increased risk for infection and disease. Health care workers (HCW) should be particularly aware of the need for preventing transmission of M. tuberculosis in

settings in which persons infected with HIV might be encountered. Transmission of M. tuberculosis is a risk in health care settings.Health care associated transmission of M. tuberculosis has been linked to contact with persons with TB during aerosol-generating procedures including bronchoscopy,endotracheal intubation,suctioning, other respiratory procedures, open abscess irrigation, autopsy, sputum induction and aerosol treatments that induce coughing. Of the reported TB outbreaks in health care settings, multiple outbreaks involved transmission of MDR TB strains to both patients and health care workers. The majority of the patients and certain HCWs were HIV-infected, and progression to TB and MDR TB disease was rapid[14]. Factors contributing to these outbreaks included delayed diagnosis of TB disease, delay in initiation of treatment and inadequate airborne precautions, lapses in practices and precautions for cough-inducing and aerosol-generating procedures, and lack of adequate respiratory protection. One of the most important source for transmission of M.tuberculosis in health care settings is from patients with unrecognized TB disease who are not promptly handled with appropriate airborne precautions[14].

The first and most important level of TB control is the use of administrative measures to reduce the risk of transmission from TB suspects using appropriate signage advising respiratory hygiene and cough etiquette.

Cough hygiene refers to measures like 1) Covering the mouth/ nose when coughing or sneezing 2) Using tissues to contain respiratory secretions and dispose them in the nearest waste receptacle after use 3) To practice hand hygiene (e.g., hand washing with antimicrobial soap and water, alcohol-based hand rub, or antiseptic hand wash) after having contact with respiratory secretions and contaminated objects/materials. 4) Stand /sit at least 3 feet from patients[15].

If we have to control TB, we need to focus on infection control along with case detection and treatment. The general population should be made aware about the symptoms of TB. Everyone should practice strict cough hygiene so that transmission of respiratory infection is minimized. Patients diagnosed with pulmonary TB should strictly be advised isolation till he/she becomes non infectious[15]. Anti tussives may help to reduce the cough and hence may help to decrease the chances of spread of the disease. Infection control measures should be implemented in all health care settings. Legislation enforcing cough hygiene among the public and infection control measures in health care facilities with strict adherence to the legislation will definitely help to decrease the burden of TB in India.

Implementation of infection control measures will decrease the incidence of both nosocomial TB as well as drug resistant TB in the high risk and vulnerable population.

References:

1. WHO(2000), Joint Tuberculosis Programme Review, India, February 2000,Regional office for South-East Asia, New Delhi.
2. Dye C.Global epidemiology of tuberculosis.Lancet, 2006;367:938-40.
3. World Health Organisation: Global tuberculosis control: surveillance, planning, financing.Geneva: WHO; 2009
4. Central TB. Division, Directorate General of Health Services. TB India 2005. RNTCP Status report. New Delhi, India: Ministry of Health and Family Welfare; 2005

5. Wells WF: On air-borne infection study II. Droplets and droplet nuclei. Am J Hygiene, 1934:20. 611-18.
6. Participant's Manual for integrated management of adolescent and adult illness(imai) TB Infection Control Training at Health Facilities. In WHO,July 2008: 9.
7. American Thoracic Society, CDC, Infectious Disease Society of America. Diagnostic standards and classification of tuberculosis in adults and children. Am J RespirCrit Care Med 2000;161:1376-95.
8. American Thoracic Society, CDC, and Infectious Disease Society of America. Treatment of tuberculosis. MMWR 2003; 52(No.RR-11).
9. Wells WF. Aerodynamics of droplet nuclei [Chapter 3]. In: Airborne contagion and air hygiene. Cambridge, MA: Harvard University Press; 1955:13-9.
10. HatchTF : distribution and deposition of inhaled particles in respiratory tract. Bacteriol rev 1961,25:237-240
11. Loudon RG, Spohn SK. Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis 1969;99:109-111
12. Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, Nguyen CH: Outcomes of contact investigations of infectious tuberculosis patients. Am J RespirCrit Care Med 2000, 162(6):2033-2038.
13. Bauer J, Kok-Jensen A, Faurschou P, Thuesen J, Taudorf E, Andersen AB. A prospective evaluation of the clinical value of nation-wide DNA fingerprinting of tuberculosis isolates in Denmark. Int J Tuberc Lung Dis 2000;4:295-299
14. Koppaka VR, Ridzon R. Prevention and control of the nosocomial transmission of Mycobacterium tuberculosis. In: Wenzel RP, ed. Prevention and control of nosocomial infections. 4 edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:229-52.
15. Respiratory hygiene/cough etiquette in Health care settings. In: Department of health and human services, centre for disease control and prevention,Nov 2004: 1

Review Article

Sarcoidosis

Durga Balagopalan
Asst. Professor, Dept. of Pulmonary Medicine,
Malabar Medical College, Modakkallur, Kozhikode.

Sarcoidosis is a multisystem disorder of unknown origin characterized by non caseating granulomatous inflammation at sites of disease. The modern history of sarcoidosis goes back to 1899, when the Norwegian dermatologist Caesar Boeck coined the term to describe skin nodules characterized by compact, sharply defined foci of "epithelioid cells with large pale nuclei and also a few giant cells."[1] Thinking this resembled sarcoma, he called the condition "multiple benign sarcoid of the skin."[1]Ninety percent of sarcoidosis patients will present with some form of lung disease, which may be asymptomatic.

Epidemiology

Sarcoidosis affects people of all racial and ethnic groups and occurs at all ages, although it usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years.[3] The incidence of sarcoidosis varies widely throughout the world, probably because of differences in environmental exposures, surveillance methods, and predisposing HLA alleles and other genetic factors. The highest annual incidence of sarcoidosis has been observed in northern European countries (5 to 40 cases per 100,000 people).[1, 2]

Sarcoidosis is an under diagnosed disease in India. However, owing to the increasing awareness, now-a-days it is being diagnosed more frequently than a few decades ago. Most Indian patients with sarcoidosis are males and present in the fourth or fifth decade of life.[13] Amongst few estimates that are available, sarcoidosis constituted 10-12 cases per 1000 new registrations annually at a respiratory unit in Kolkata, Marwari community being at a higher risk. Another estimate at an institute in Delhi found 61.2 / 100,000 new cases.

Environmental Causes

Sarcoidosis most commonly involves the lungs, eyes, and skin. So the search for environmental causes has focused on exposures to airborne antigens. Various associations reported in different studies include

1. Emission from wood-burning stoves
2. Tree pollen[3]
3. Exposure to inorganic particles[4]
4. Insecticides[5]
5. Moldy environments[5,6]
6. Metal working[6]
7. Fire fighting[7]
8. Handling of building supplies[8]

Mycobacterial and Propionibacterium acne DNA and RNA have been recovered from sarcoid tissue by polymerase-chain-reaction technique.

Genetic Features

Familial sarcoidosis was first reported in 1923 in two affected sisters.[16] The concordance appears to be higher in monozygotic twins than in dizygotic twins.[17]

Genetic Associations

HLA genes

1. HLA-B8
2. HLA-DRB1 and DQB1
3. HLA-DQB1*0201 and HLA-DRB1*0301

Non-HLA candidate genes

1. Butyrophilin-like 2 (BTNL2) gene on chromosome 6p
2. Chromosome 3p
3. Chromosome 5q11.2
4. Chromosome 5p15.2.

Immunopathogenesis

The development and accumulation of granulomas constitute the fundamental abnormality in sarcoidosis[9]. Granulomas are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. Main feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of granulomas. These activated CD4+ cells differentiate into type 1 helper T (Th1)-like cells and secrete predominantly interleukin-2 and interferon-γ, augment macrophage Tumor necrosis factor α (TNF-α) production, and amplify the local cellular immune response.[10] Although granulomas may resolve with little consequence, pulmonary fibrosis occurs in 20 to 25% of patients with sarcoidosis. Overproduction and unopposed activity of Matrix metalloproteinase(MMP), particularly matrix metalloproteinase 8 and 9 initiates extracellular-matrix breakdown and remodeling. A shift from cytokines produced by Th1 cells (mainly interleukin-2 and interferon-γ) to cytokines produced by type 2 helper T (Th2) cells (mainly interleukins 4, 10, and 13) also appears to be central to the development of fibrosis.[11]Alveolar macrophages activated in the context of Th2 cytokines produce high levels of fibronectin and the CC motif ligand 18 (CCL18) chemokine[12], which up-regulates collagen production by lung fibroblast.

Clinical Features

Sarcoidosis often comes to attention when abnormalities are detected on a chest radiograph during a routine screening examination. Systemic symptoms such as fatigue, night sweats, and weight loss are common. The organ system that is most affected varies with the given patient (Table 1). Löfgren's syndrome, an acute presentation consisting of arthritis, erythema nodosum, and bilateral hilar adenopathy, occurs in 9 to 34% of patients.[1] Erythema nodosum is observed predominantly in women, but marked ankle periarticular inflammation or arthritis without erythema nodosum is more common in men.

Diagnosis

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs of non caseating epithelioid-cell granulomas in the absence of organisms or particles.[1]

The chest radiograph is abnormal in more than 90 percent of known cases and carries prognostic information

Radiologic Classification

1. Stage 0 (5 to 10%) - A normal chest radiograph, with extrapulmonary manifestations.

2. Stage I (40 %) - hilar adenopathy without evidence of interstitial infiltrates. Often, hilar adenopathy has a discrete, symmetric "potato node" appearance, and is accompanied by right paratracheal lymphnodes.Calcification of hilar lymph nodes is uncommon.

3. Stage II (30 to 50 %) bilateral hilar adenopathy and pulmonary infiltrates (Infiltrates can be fine linear markings and small reticulonodules, particularly in mid- and upper lung zones. Occasionally, the infiltrates consist of discrete nodules or areas of fluffy "alveolar" consolidation. A miliary pattern may also be seen).[20]

4. Stage III Pulmonary infiltrates without bilateral hilar adenopathy

5. Stage IV Extensive pulmonary fibrosis and scarring

Investigations

The Kveim-Siltzbach test has been used for many years in the diagnosis of sarcoidosis. The test is performed by injecting homogenate of human sarcoid tissue extract intradermally. The papule that develops at the site of injection after 4 weeks is biopsied. This test is now used less often for several reasons. First, no commercially available preparation of the antigen exists. Second, the use of human tissue extracts for clinical purposes presents many constraints. Third, each new Kveim-Siltzbach preparation requires validation in vivo.

Sarcoidal granulomas produce angiotensin-converting enzyme (ACE), and ACE levels are elevated in 60% of patients with sarcoidosis. However, the value of serum ACE levels in diagnosing or managing sarcoidosis remains controversial. Measurement of serum ACE levels lacks sensitivity and specificity.

A diagnosis of sarcoidosis is certain without biopsy when patients present with Löfgren's syndrome. In all other cases, a biopsy specimen should be obtained from

Table 1 - Organ Involvement

Organ System (Percent Clinical Disease)	Major Clinical Features
Pulmonary (>90%)	Restrictive and/or obstructive disease, fibrocystic disease, bronchiectasis
Upper respiratory tract and oral cavity (5-10%)	Hoarseness, laryngeal or tracheal obstruction, nasal congestion, sinusitis
Ocular (20-30%)	Anterior and posterior uveitis, chorioretinitis, conjunctivitis, optic neuritis
Skin (20-30%)	Erythema nodosum, chronic nodules and plaques, lupus pernio, alopecia
Hepatic/Abdominal (10-20%)	Hepatosplenomegaly, jaundice, cirrhosis, retroperitoneal lymphadenopathy
Cardiac (5-10%)	Arrhythmias, heart block, cardiomyopathy, sudden death
Neurologic (5-10%)	Facial and other cranial neuropathies (e.g., Bell's palsy) aseptic meningitis, brain mass, seizures, obstructing hydrocephalus, hypothalamic hypopituitarism, myelopathy, polyneuropathy
Exocrine gland (10-20%)	Salivary, lacrimal, and parotid gland enlargement, sicca syndrome
Hematologic (20-30%)	Peripheral or retroperitoneal lymphadenopathy, splenomegaly, hypersplenism, anemia, lymphopenia
Joints and musculoskeletal (10-20%)	Polyarthritis, Achilles tendinitis, heel pain, polydactylitis, bone cysts, myopathy
Endocrine (10-30%)	Hypercalciuria, hypercalcemia, hypopituitarism, diabetes insipidus
Renal (<5%)	Renal calculi, nephrocalcinosis, renal failure
Genitourinary (<5%)	Ovarian or uterine mass, dysmenorrhea, testicular mass, epididymitis
Psychosocial manifestations (30-60%)	Depression

the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva. If diagnosis requires pulmonary tissue, transbronchial biopsy by means of bronchoscopy has a diagnostic yield of at least 85% when multiple lung segments are sampled.[1]

BAL can be used as an adjunctive measure to support the diagnosis of sarcoidosis by demonstrating a reduced number of CD8 cells and an elevated CD4/CD8 ratio. EBUS-TBNA allows real-time ultrasound localization and aspiration of hilar and mediastinal lymph nodes.[18]

Recently, several reports suggested that 18F-fluorodeoxyglucose positron-emission tomography (^{18}FDG PET) may be useful in assessing the extent of organ involvement and indicating the organs that are candidates for diagnostic biopsy.[14]

Biomarkers of Disease Activity

To date, practical and reliable biomarkers of disease activity have not been identified. Chitotriosidase, an enzyme involved in the degradation of chitin, is expressed by activated macrophages. Certain studies showed significantly higher levels in patients with active sarcoidosis than in those with inactive sarcoidosis. Recent evidence suggests that IL-2 receptor is elevated in serum and BAL fluid of patients with sarcoidosis and that it may have prognostic value in sarcoidosis.[18]

Treatment

In view of the high rate of spontaneous remission and significant side effects, treatment is not indicated for: [15]

1. Asymptomatic stage I disease;

2. Asymptomatic stage II disease with mildly abnormal lung function and stable disease (measured 3–6-monthly);

3. Asymptomatic stage III disease with mildly abnormal lung function and stable disease (measured 3–6-monthly).

Treatment should be considered for patients with Pulmonary Sarcoidosis if :

1. Deteriorating lung function over 3–6 month intervals

2. Deteriorating radiological changes

3. Significant pulmonary symptoms of cough, shortness of breath, chest pain or haemoptysis.[15]

Table 2 - Indications for treatment of Sarcoidosis with systemic agents[20]

- Threatened organ failure—severe ocular, cardiac, or neurological disease
- Progressive or persistent pulmonary disease
- Uveitis unresponsive to topical corticosteroids
- Persistent hypercalcemia, renal or hepatic dysfunction
- Palpable splenomegaly or hypersplenism
- Severe myopathy
- Disfiguring skin disease
- Painful lymphadenopathy
- Severe fatigue and weight loss

Lofgren syndrome is usually managed with bed rest and nonsteroidal anti-inflammatory drugs.

Oral corticosteroids are the first line of therapy in patients with progressive disease (determined by radiology or on lung function), significant symptoms or extrapulmonary disease requiring treatment. BTS guidelines suggest a dose of 0.5 mg/kg/day of oral prednisolone and as patient responds, the dose should then be reduced gradually to a maintenance dose which will control symptoms and disease progression and should be used for a period of 6-24 months. Current British ILD guidelines recommend other immunosuppressive agents when corticosteroids alone are not effective, or when side-effects are unacceptable,then methotrexate is the usual choice. Lung transplantation should be considered in end-stage pulmonary sarcoidosis. Bisphosphonates should be used to minimise steroid induced osteoporosis. Inhaled corticosteroids may be considered for symptom control (cough) in a subgroup of patients.[15]

TNF inhibitors have been investigated for the treatment of sarcoidosis. In a preliminary clinical trial of patients assessing the efficacy of etanercept, treatment failure was observed in nearly 65% of patients. Judson and colleagues found infliximab was effective for the treatment of both extrapulmonary and chronic steroid-dependent pulmonary sarcoidosis.[18] Patients currently are being recruited for clinical trials evaluating the safety and efficacy of ustekinumab and golimumab, a TNF- α antagonist, in the treatment of chronic sarcoidosis.[19]

Reference

1. Michael C. Iannuzzi, M.D., Benjamin A. Rybicki, Ph.D., and Alvin S. Teirstein, M.D. N Engl J Med 2007; 357:2153-2165November 22, 2007DOI: 10.1056/ NEJMra071714
2. Pietinalho A, Hiraga Y, Hosoda Y, Lofroos AB, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan: a comparative epidemiological study.Sarcoidosis 1995;12:61-67
3. Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. Epidemiol Rev 1983;5:124-156
4. Rybicki BA, Amend KL, Maliarik MJ, Iannuzzi MC. Photocopier exposure and risk of sarcoidosis in African-American sibs. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:49-55
5. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med 2004;170:1324-1330
6. Kucera GP, Rybicki BA, Kirkey KL, et al. Occupational risk factors for sarcoidosis in African-American siblings. Chest 2003;123:1527-1535
7 .Prezant DJ, Dhala A, Goldstein A, et al. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. Chest 1999;116:1183-1193

8. Barnard J, Rose C, Newman L, et al. Job and industry classifications associated with sarcoidosis in A Case-Control Etiologic Study of Sarcoidosis (ACCESS). J Occup Environ Med 2005;47:226-234

9. Agostini C, Adami F, Semenzato G. New pathogenetic insights into the sarcoid granuloma.Curr Opin Rheumatol 2000; 12:71-76

10. Zissel G, Prasse A, Muller-Quernheim J. Sarcoidosis -- immunopathogenetic concepts.Semin Respir Crit Care Med 2007;28:3-14

11. Wahlstrom J, Katchar K, Wigzell H, Olerup O, Eklund A, Grunewald J. Analysis of intracellular cytokines in CD4+ and CD8+ lung and blood T cells in sarcoidosis. Am J Respir Crit Care Med 2001;163:115-121

12. Prasse A, Pechkovsky DV, Toews GB, et al. A vicious circle of alveolar macrophages and fibroblasts perpetuates pulmonary fibrosis via CCL18. Am J Respir Crit Care Med2006;173:781-792

13. Sharma Sk, Mohan A. Sarcoidosis: Global scenario & Indian perspective. Indian J Med Res. 2002;116:221-47

14. Nunes H, Brillet PY, Valeyre D, Brauner MW,Wells AU. Imaging in sarcoidosis. Semin Respir Crit Care Med 2007;28:102-120

15. BTS Guidelines for ILD Thorax 2008;63;v1-v58

16. Martenstein H. Knochveranderungen bei lupus pernio. Z Haut Geschlechskr 1923;7:308-308

17. Familial associations in sarcoidosis: a report to the Research Committee of the British Thoracic and Tuberculosis Association. Tubercle 1973;54:87-98

18. Morgenthau AS. Recent advances in Sarcoidosis. CHEST 2011; 139(1):174-182

19. Judson MA , Baughman RP , Costabel U , et al ; CentocorT48 Sarcoidosis Investigators . Effi cacy of infl iximab in extrapulmonarysarcoidosis: results from a randomised trial . Eur Respir J . 2008 ; 31 (6): 1189 - 1196.

20. Fishman's Pulmonary Diseases and Disorders 4th Edition Part Vll :67,pg no:1132-39

Review Article

Treatment of Pulmonary Hypertension- An Overview

Jyothi E

Associate Professor, Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode

Pulmonary Hypertension (PH) has been defned as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterisation (RHC)[1]. It is characterised by progressive and sustained increase in pulmonary vascular resistance, that will eventually lead to right ventricular failure. It is a life threatening condition if not treated. It mainly involves the small pulmonary arteries and results in unregulated vasoconstriction, vascular smooth muscle cell proliferation and vascular remodelling.

The common causes of pulmonary hypertension are left heart diseases and lung diseases. But significant research in the field of pulmonary hypertension has been done in pulmonary arterial hypertension (PAH) group and the new treatment options that is available now is mainly recommended for this group.

Classification

World Health Organisation classifies pulmonary hyper tension into 5 group based on pathological, pathophysiological and therapeutic characteristics. The classification that is followed now is the Dana Point classification of 2008[2]. Patients in group I are categorised as pulmonary arterial hypertension, while the remaining four groups are categorised as pulmonary hypertension.

Epidemiology

The reported prevalence of PAH from pulmonary hypertension registries is 15 cases/ million adult population[3].Idiopathic Pulmonary Arterial Hypertension(IPAH) is even rare with a frequency of 1-2 cases/million population[4]. Any age group can be affected, but IPAH is more common in females in the third decade of life and in males in the fourth decade of life.

The prevalence of pulmonary hypertension in advanced COPD is 50.2% in a study done in France among patients waiting for lung volume reduction surgery, and is usually of mild severity[5]. Up to 32% of patients with advanced idiopathic pulmonary fibrosis have PH[6]. Studies have shown that patients with combined pulmonary fibrosis and emphysema (CPFE) have higher prevalence of pulmonary hypertension[7].

Table 1: Updated clinical classifcation of pulmonary hypertension (Dana Point, 2008)

1 Pulmonary arterial hypertension (PAH)

1.1 Idiopathic

1.2 Heritable 1.2.1 BMPR2, 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia) 1.2.3 Unknown

1.3 Drugs and toxins induced

1.4 Associated with (APAH) 1.4.1 Connective tissue diseases 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.4.6 Chronic haemolytic anaemia

1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease

2.1 Systolic dysfunction

2.2 Diastolic dysfunction

2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/ or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension(CTEPH)

5 PH with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: myeloproliferative disorders,splenectomy.

5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis,lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 Activin Receptor like Kinase 1 gene,

BMPR2- Bone Morphogenetic Protein Receptor, type2, APAH-Associated Pulmonary Arterial Hypertension

Pathogenesis

Pathogenesis of pulmonary hypetension is multifactorial, and not fully understood. The normal pulmonary circulation is a low resistance system which can accommodate the entire cardiac output. This is done by dilation of the existing vasculature and recruitment of unused vessels.

Endothelial dysfunction plays a key role in the pathogenesis of pulmonary hypertension. The key mediators produced by pulmonary endothelium that play a significant role in pulmonary hypertension pathogenesis are endothelin, prostacyclin and nitric oxide (NO). Prostacyclin and nitric oxide are pulmonary vasodilators and endothelin is a pulmonary vasoconstrictor. An imbalance between vasodilators and vasoconstrictors is a key contributor to the initiation and progression of the disease. The present day targeted treatment of pulmonary hypertension acts by modifying this vasoconstrictor- vasodilator mechanism.

The other proposed mechanisms of pulmonary hypertension are increased production of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and serotonin produced by platelets[8].

Pulmonary vascular resistance is increased by three mechanisms. These are vasoconstriction, remodelling of the pulmonary vessel and thrombosis in situ.

The development of pulmonary hypertension in lung disease is also due to multiple mechanisms. The commonly described mechanisms are hpoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of pulmonary vascular bed, inflammation and toxic effects of cigarette smoke. As in all the other groups of PH, an imbalance between the endothelium derived vasoconstrictors and vasodilators has also been proposed.

"Out of proportion" pulmonary hypertension

Out of proportion pulmonary hypertension is defined as an unjustified degree of pulmonary hypertension that occurs in patients with chronic lung disease. Some patients with minor pulmonary impairment in pulmonary function tests and CT thorax , were found to have high pulmonary artery pressure. This could not be solely explained by hypoxia or loss of pulmonary vascular bed. An arbitrary value of > 35mm Hg mean pulmonary artery pressure has been used to define out of proportion PH[9].

Diagnosis

Evaluation of a patient with suspected pulmonary hypertension includes investigations to confirm the diagnosis

and to find out the group to which the patient belongs. The symptoms of pulmonary hypertension are nonspecific and include breathlessness, fatigue, weakness, angina and syncope. The physical signs are left parasternal heave, an accentuated pulmonic component of second heart sound, a pan systolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary insufficiency.

The common investigations that are done include electrocardiogram, echocardiography and right heart catheterisation to confirm the diagnosis. The other investigations that may be done to classify and find out the etiology of pulmonary hypertension include chest radiography, pulmonary function testing including spirometry, DLCO and blood gas analysis; ventilation perfusion lung scan, high resolution computed tomography, contrast enhanced CT of thorax and pulmonary angiography. The other investigations that may be done for etiological diagnosis are abdominal ultrasonogram to detect portal hypertension; blood tests and immunology to detect connective tissue disorders, HIV infection and hepatitis.

Treatment

In the past few years treatment of pulmonary hypertension has undergone tremendous improvement, with many new drugs being approved for treatment. Regardless of the etiology of pulmonary hypertension, general supportive treatment is similar for all patients. Supportive treatment is aimed at improving symptoms and quality of life. The basic treatment of group2,3,4, and 5 pulmonary hypertension includes treatment of the primary disease. Specific therapy or advanced therapy is directed at the pulmonary hypertension itself, rather than the underlying cause of pulmonary hypertension. The drugs available for specific therapy includes prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors and rarely calcium channel blockers. But currently

Table 2 : Functional classifcation of pulmonary hypertension modifed after the New York Heart Association functional classifcation according to WHO

Class I	Patients with pulmonary hypertension but without resultinglimitation ofphysical activity. Ordinaryphysical activitydoesnotcauseunduedyspnoeaorfatigue,chest pain, or near syncope.
Class II.	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carryoutany physicalactivity withoutsymptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

specific pulmonary vasodilators which mainly target endothelial dysfunction in pulmonary hypertension, have been proven beneficial in group I PH only.

Assessment of therapy

The baseline assessment of severity should be done prior to starting treatment. This is essential because the response to therapy is measured as the change from baseline. Disease severity is evaluated by assessing functional impairment and hemodynamic derangement. Objective evaluation of functional impairment includes a 6 minute walk test (6MWT) and the WHO functional class (WHO-FC)[10]. Pulmonary artery systolic pressure and right ventricular function is estimated by echocardiography and right heart catheterisation.

General supportive treatment

General supportive measures of treatment are common for all groups of patients.

Physical activity : Heavy physical activity should be avoided in patients with PH, as this can lead to severe breathlessness, exertional dizziness and chest pain. Patients should be encouraged to go for physical activity within symptom limits. Exercise training appears to be beneficial as this prevents physical deconditioning and muscular atrophy.

Pregancy: Pregnancy results in increase in cardiac output and blood volume. The ability of the heart to accommodate the increased cardiovascular load is limited in patients with pulmonary hypertension. Pregnancy is associated with 30-56% mortality in patients with PAH, and so PAH is a contraindication for pregnancy[11].

Travel: Patients with WHO-FC III and IV, and those with arterial PaO2 below 60mmHg should be advised to receive supplemental oxygen during flight travel.

Prevention of infection: Patients with PAH are susceptible to develop pneumonia and it can be the cause of death in up to 7% of patients[12]. So pulmonary infections should be promptly diagnosed and treated. Vaccination against influenza and pneumococcal pneumonia is recommended.

Oral anticoagulants: Patients with PH are at increased risk of intrapulmonary thrombosis and thromboembolism. Other risk factors for the development of thrombosis include heart failure, dilated heart chambers and immobility. Definite recommendation for oral anticoagulants is for patients with IPAH, heritable PAH, drug induced PAH and group 4 pulmonary hypertension. Preferred drug for oral anticoagulation is warfarin , with a therapeutic goal of international normalised ratio (INR) of 2-3.

Supplemental oxygen: Long term oxygen therapy (LTOT) is the cornerstone of treatment for patients with group 3 PH. As hypoxemia can aggravate pulmonary hypertension by increasing pulmonary vasoconstriction , supplemental oxygen should be considered for all patients with severe hypoxemia[13].

Digoxin : In patients with right heart failure secondary to pulmonary hypertension, myocardial contractility may improve with cardiac gylcosides. But the only definite indication for digoxin therapy is the presence of supraventricular tachyarrhythmia like atrial flutter or fibrillation to slow down the ventricular rate. As most of these patients have hypoxemia and diueretic induced hypokalemia , digoxin toxicity is more likely in these group of patients.

Diuretics: Diuretics improve the symptoms and signs of right hear failure. Dose can be modified based on individual patient requirement.

Primary therapy

Primary therapy is directed at the underlying cause of pulmonary hypertension. In case of group I (PAH), there is no effective primary therapy, as the definite cause of pulmonary hypertension is not known in majority of patients. Group 2 patients develop pulmonary hypertension secondary to left heart disease. Primary therapy of the underlying heart disease is the best option available for this group of patients. Group 3 patients includes patients with lung disease and/ or hypoxia. Primary therapy consists of treating the underlying lung disease and correction of hypoxemia with supplemental oxygen. Long term oxygen therapy is the only treatment available for this group of patients with proven mortality benefit.

Patients with group 4 PH have pulmonary hypertension secondary to thromboembolic occlusion of

the pulmonary vasculature. Anticoagulants is the primary medical therapy available for this group of patients aimed at preventing recurrent pulmonary embolism. Surgical thromboendarterectomy is the definite treatment modality for selected patients with thromboembolic obstruction of the proximal pulmonary arteries. In group 5 patients primary treatment is directed against the underlying cause of pulmonary hypertension.

Specific therapy

Specific therapy is directed against pulmonary hypertension and not against the underlying cause of pulmonary hypertension. Three major groups of drugs are available for specific therapy. These are prostanoids, endothelial receptor antagonists and phosphodiesterase -5 inhibitors. Calcium channel blockers were used for the treatment of pulmonary hypertension even before the present group of targeted drugs were approved. Specific therapy is the only available treatment modality for patients with group I PH as primary therapy is not available for this group. But treatment of patients with pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis with vasodilators can result in pulmonary oedema and should be used with caution[14].

In group 2 patients advanced therapy should be avoided if possible. For group 3 patients, present guidelines do not favour specific therapy except in the context of clinical trials. Specific therapy may also be tried for those patients who remain WHO-FC III or IV in spite of treatment of underlying lung disease and oxygen therapy, especially if the severity of PH is out of proportion to the severity of lung disease . These vasodilators will reduce pulmonary artery pressure, but can worsen ventilation perfusion mismatch. Vasodilators can inhibit hypoxic pulmonary vasoconstriction especially in group 3 patients. So specific therapy can be given to this group of patients only under close monitoring.

In group 4 patients also specific therapy may be considered for those patients who remain in WHO FC III or IV in spite of anticoagulation and thromboendarterectomy.

Calcium channel blockers(CCB): Pulmonary vasoconstriction plays a significant role in the pathogenesis of pulmonary hypertension. So vasodilators like calcium channel blockers has been used for the treatment of pulmonary hypertension. The CCBs that have been commonly used are nifedipine and diltiazem. The recommended dosages are very high. Nifedipine is given in the dose of 90-180mg/day (upto240mg) and diltiazem is given in the dose of 240-720mg/day (up to 900mg). Systemic hypotension and limb oedema can occur at these dose. CCBs should be used only when there is positive vasodilator response. Agents used for vasoreactivity testing are nitric oxide, intravenous epoprostenol or intravenous adenosine. A positive acute response is defined as a reduction in mean pulmonary artery pressure of $\geq$ 10mmHg or an absolute value of mean pulmonary artery pressure $\leq$ 40mmHg with an increased or unchanged cardiac output. Generally only about 10% of IPAH patients show a positive acute vasoreactive response. But even with a positive response, only half of them show a positive long term response to CCBs. Acute vasoreactivity testing is not recommended in clinical groups 2,3,4 and5[1]

Prostanoids

Prostacyclin is a natural prostanoid produced by vascular endothelial cells and its level is found to be reduced in pulmonary hypertension. It is a potent vasodilator, inhibits platelet aggregation and has antiproliferative action.

Epoprostenol: is a synthetic prostacyclin and is available as a freeze dried preparation. It has a short half life of 3-5 minutes and should be administered as continuous intravenous infusion with an infusion pump. The dose varies from 20-40ng/kg/min. It is reserved for patients with severe PH especially those with IPAH. The common side effects include headache, flushing, jaw pain, diarrhoea and vomiting. More serious complications are infusion pump and catheter related including bleeding, site infection, bacteremia and sepsis.

Iloprost : Iloprost is a chemically stable prostacyclin analogue available for oral, intravenous and inhaled use. Being available for inhaled route is attractive as it avoids

the systemic effects of the drug.

Beraprost sodium : It is the first biologically stable oral prostacyclin analogue available for treatment of pulmonary hypertension.

Trepostinil: It is another analogue of prostacyclin which is stable at room temperature. It can be given by both intravenous and subcutaneous route. This is approved for treatment of class II, III and IV patients with PAH.

Endothelin receptor antagonists

Increased level of endothelin-1 has been seen in plasma and lung tissue of patients with pulmonary hypertension[15]. Endothelin is a vasoconstrictor and mitogen for vascular smooth muscle. It acts by binding to ETA and ETB receptors. ETA receptor stimulation results in vasoconstriction and vascular smooth muscle cell proliferation and ETB receptor stimulation results in vasodilation and it has antiproliferative action[16].

Bosentan: Bosentan is an orally active dual (ETA and ETB) endothelin receptor antagonist. It is the first molecule of this group available for treatment of pulmonary hypertension. In the BREATHE 1 trial of bosentan 213 patients with PAH with WHO FC III and IV were randomised to receive either placebo or 62.5 mg of bosentan twice daily for 4 weeks. After that bosentan was given in the dose of 125mg or 250mg twice daily for 12 weeks. After 16 weeks there was an increase in 6 minute walk distance of 44m compared to placebo. An improvement in Borg dyspnoea index and WHO FC was also seen[17].

In the EARLY trial, PAH patients with WHO FC II were given either bosentan or placebo. In this study also there was a significant reduction of pulmonary vascular resistance in patients treated with bosentan[18].

Increase in aminotransferase has been seen in patients treated with bosentan . So monthly liver function test monitoring should be done in patients receiving bosentan.

Ambrisentan: Ambrisentan is a selective ETAreceptor blocker and it has the advantage of once daily administration. In ARIES 1(5or 10mg) and ARIES 2 (2.5 or 5mg) trial patients with PAH were randomised to receive ambrisentan or placebo orally once daily for 12 weeks[19]. It was found that ambrisentan improves exercise capacity in patients with PAH. In ARIES 3 trial, ambrisentan was given to patients belonging to all groups of pulmonary hypertension[20]. Patients received 5mg ambrisentan once daily for 24 weeks. Primary end point was change in 6 minute walk distance from baseline. There was an increase in 6 minute walk distance of 21m from baseline in the overall population. However , increase in 6MWD was not observed in several non-group 1 PH patients.

An increased incidence of peripheral oedema has been reported , but hepatotoxicity is less for ambrisentan.

Phosphodiesterase 5 inhibitor

Inhibition of type 5 phosphodiesterase leads to increased concentration of cyclic guanosine monophosphate (cGMP) in vascular smooth muscles resulting in vasodilation. The two available drugs in this group for treatment of pulmonary hypertension at present are sildenafil and tadalafil.

Sildenafil: Sildenafil is an oral phosphodiesterase inhibitor. It is a potent pulmonary selective vasodilator. In the SUPER study, 278 patients with PAH (IPAH, connective tissue disease associated or those with congenital systemic to pulmonary shunts) received 20, 40 or 80mg sildenafil orally thrice daily[21]. There was a significant increase in 6 minute walk distance of 45m, 46m and 50m respectively in the three dosage groups at 12 weeks. After one year of treatment there was an improvement of 6MWT distance of 51m in patients receiving sildenafil. FDA has approved sildenafil for patients with PAH in any functional class at a dose of 20mg three times daily.

Sildenafil improves pulmonary hemodynamics in patients with PH secondary to COPD. But it reduces arterial oxygenation due to inhibition of hypoxic pulmonary vasoconstriction. In the study done by Isabel Blanco et al, it was found that at rest sildenafil worsened arterial oxygenation due to greater ventilation-perfusion mismatch[22]. But there was no further worsening of arterial oxygenation with exercise. In a study done on a small number of patients

with interstitial lung disease associated pulmonary hypertension by Corte TJ et al, it was found to improve 6MWT distance[23]. More randomised controlled trials are required to study the efficacy of sildenafil in group 3 pulmonary hypertension.

Tadalafil : Tadalafil is a selective phosphodiesterase 5 inhibtor. It is an oral drug and has the advantage of once daily dosing. Recommended dose is 40mg once daily. In the PHIRST and PHIRST 2 studies , it was shown to improve 6MWT distance.

Combination therapy:

Two or more drugs which acts on different pathways can be used in patients with incomplete response to a single agent. The drugs used for combination therapy are endothelin receptor antagonists, phosphodiesterase 5 inhibitors, prostanoids and other novel therapeutic agents. This is similar to systemic hypertension where multiple agents with different mechanisms of action can be used.

BREATHE -2 trial showed a better haemodynamic effect by combining epoprostenol and bosentan[24]. Inhaled ilaprost was combined with bosentan in the STEP-1 study , and it was found to increase the 6MWT distance marginally[25]. Combination therapy is reserved for patients not responding adequately to monotherapy.

New drugs

Riociguat: Riociguat is a novel soluble guanylate cyclase stimulator being investigated for treatment of pulmonary arterial hypertencion, and chronic thromboembolic pulmonary hypertension. It was found to significantly improve exercise capacity in patients with pulmonary arterial hypertension in the PATENT 1 study[27]. In another study, the CHEST-1 oral riociguat significantly improved exercise capacity in patients with chronic thromboembolic pulmonary hypertension.

Imatinib mesylate: It is a tyrosine kinase receptor blocker, and inhibits platelet derived growth factor signalling. It inhibits vascular smooth muscle cell proliferation. In the recently published IMPRES study, imatinib mesylate was found to improve exercise capacity and hemodynamics in patients with advanced PAH[26]. But there were significant serious adverse events requiring discontinuation of the drug. So further studies are required to investigate the long term safety and efficacy of this drug.

Surgical Treatment

Atrial septostomy: Patients with Eisenmenger's syndrome and those with IPAH with patent foramen ovale had a better prognosis compared to those without a patent foramen ovale. This observation supported the idea of atrial septostomy for patients with disabling right heart failure. The creation of an inter atrial right to left shunt can decompress the right cardiac chambers. Recommended technique is graded balloon dilation atrial septostomy. Atrial septostomy should be regarded as a palliative procedure in patients with recurrent syncope or right heart failure in spite of maximal medical therapy.

Lung transplantation: Patients who do not have an adequate clinical response in spite of aggressive medical management should be considered for lung transplantation. Double lung and heart lung transplantation are the preferred procedures. Survival after lung transplantation is 65%, 55% and 44% after 1 year, 3 years and 5 years respectively.

Conclusion

At present pulmonary hypertension is an incurable condition with poor prognosis. As the symptoms and signs are nonspecific, the diagnosis is often delayed. All patients diagnosed with pulmonary hypertension should be evaluated in detail to rule out an underlying cause that can be successfully treated. In the last decade several drugs have been available for targeted treatment of pulmonary hypertension . The new drugs have significantly improved the survival of patients with pulmonary hypertension. Recently increasing data are available regarding the use of combination therapy for treating PH. However more research is required to assess the safety and efficacy of these drugs in long term use.

Reference

1. Galie N, HoeperMM,Humbert M et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC), endorsed by the International Society of Heart and Lung Transplantation(ISHLT). Eur Heart J 2009;30:2493-537
2. Gerald Simonneau, Ivan M Robbins, Maurice Beghetti- Updated clinical Classification of Pulmonary Hypertension. JACC, vol 54, No.1 Suppl.S, June 30, 2009, S43-54
3. Humbert M, Sitbon O, Chaouat A et al. Pulmonary arterial hypertension in France: results from a national registry.Am J RespirCrit Care Med. 2006 May 1;173(9):1023-30.
4 Robyn J. Barst. Pulmonary hypertension: Past, present and future. Ann Thorac Med. 2008 Jan-Mar; 3(1): 1-4.
5. Thabut G, Dauriat G, Stern JB , Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest. 2005 May;127(5):1531-6.
6. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006 Mar;129(3):746-52.
7. Cottin V, Nunes H, Brillet PY, Delaval P. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005 Oct; 26(4) : 586-93.
8. Hervé P, Launay JM, Scrobohaci ML, Brenot F, Increased plasma serotonin in primary pulmonary hypertension. Am J Med. 1995 Sep;99(3):249-54.
9. SergioHarari, Out of Proportion Pulmonary Hypertension: A Paradigm for Rare Diseases. Chest 2012; 142(5):1087-1088
10. J Simon R Gibbs, Recommendations in the management of pulmonary hypertensionin clinical practice. Heart 2001; 86(suppl 1) 1-13
11. Kiely DG, Condliffe R, Webster V, Mills GH Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG. 2010 Apr;117(5):565-74
12. Nazzareno Galiè, , Adam Torbicki, Robyn BarstGuidelines on diagnosis and treatment of pulmonary arterial hypertension The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology Eur Heart J (2004) 25 (24): 2243-2278.
13. Jan Zielinski, MiroslawTobiasz; Effects of Long term Oxygen Therapy on Pulmonary Hemodynamics in COPD patients: A 6 Year Prospective Study. Chest 1998; 113(1):65-70
14. D. Montani, L. C. Price, P. Dorfmuller.Pulmonary veno-occlusive diseaseERJJanuary 1, 2009vol. 33 no. 1 189-200
15. Patrice Cacouba, , Richard Dorentb, Patrick Nataf, Endothelin-1 in the lungs of patients with pulmonary hypertension;Cardiovasc Res (1997) 33 (1): 196-200.
16. Domenic A Sica, Endothelin receptor Antagonism. What does the Future Hold? Hypertension; 2008; 52:460-61
17. Lewis J. Rubin, M.D., David B. Badesch, M.D., Bosentan Therapy for Pulmonary Arterial Hypertension ,N Engl J Med 2002; 346:896-903March 21, 2002
18. Galiè N, Rubin Lj, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial.Lancet. 2008 Jun 21;371(9630):2093-100
19. Galiè N, Olschewski H, Oudiz RJ ; Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008 Jun 10;117(23):3010-9.
20. Badesch DB, Feldman J, Keogh A, ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension CardiovascTher. 2012 Apr;30(2):93-9.
21. Galiè N, Ghofrani HA, Torbicki A, Barst RJ; Sildenafil citrate therapy for pulmonary arterial hypertension, N Engl J Med. 2005 Nov 17;353(20):2148-57.

22. Isabel Blanco, Elena Gimeno, Phillip A; "Hemodynamic and Gas Exchange Effects of Sildenafil in Patients with Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension", American Journal of Respiratory and Critical Care Medicine, Vol. 181, No. 3 (2010), 270-278.

23. Corte TJ, Gatzoulis MA, Parfitt L, Harries C, Wells AU, Wort SJ.; The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease. Respirology. 2010 Nov;15(8):1226-

24 Humbert M, Barst RJ, Robbins IM, Channick RN; Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. EurRespir J. 2004 Sep;24(3):353-9. (combination)

25. Vallerie V. McLaughlin, Ronald J. Oudiz, Adaani Frost, "Randomized Study of Adding Inhaled Iloprost to Existing Bosentan in Pulmonary Arterial Hypertension", American Journal of Respiratory and Critical Care Medicine, Vol. 174, No. 11 (2006), pp. 1257-1263. (STEP-1)

26. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, Imatinibmesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 2013 Mar 12;127(10):1128-38.

27. Ghofrani HA, Galiè N, Grimminger F, Grünig E, Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013 Jul 25;369(4):330-40.

Original Article

Acute Undifferentiated Febrile Illness Progressing to Multi Organ Dysfunction Syndrome: A Diagnostic Dilemma in Critical Care

Namrata Maheswari*, Amit Kumar Mandal**

*Clinical Associate, ** Director, Department of Pulmonology and Critical Care Medicine,

Fortis Hospital, Mohali, Punjab 160062.

Abstract

Objective: There has been a recent surge in patients presenting to critical care units with acute undifferentiated febrile illness (AUFI) rapidly progressing to multi organ dysfunction syndrome (MODS). There has been paucity of literature on these patients in Northern part of India. We studied the clinical presentation, complications, and outcome of these patients in a tertiary care hospital in north India.

Materials & Methods: A retrospective observational study of patients admitted in Medical ICU of Fortis Hospital, Mohali with AUFI & MODS over July 2012 to October 2012. Detailed history , examination, laboratory parameters, complications and outcomes were studied.

Results: A total of 40 cases were studied. The final diagnosis were leptospirosis (35%), Scrub typhus (27.5%), Dengue (17.5%), Influenza A (2.5%) and unknown etiology (17.5%). Mean age of patients was 44.5 years (22 years to 67 years) and males (65%) outnumbered females (35%). There was no correlation with common sources like working in farm lands, contact with animals and other epidemiological risk factors. Primary symptoms at the time of presentation were fever (100%), flu like symptoms (87.5%) and altered sensorium (48.5%). All patients progressed to MODS requiring intensive care and were further complicated with secondary nosocomial infections in ICU. Respiratory complications were most common in our study (100%). Several cases presented with severe icteric disease and renal failure (74.5% & 60.5% respectively). Coagulation disorders (84%) especially thrombocytopenia was common. Neurological manifestations were seen in 35% of our cases, three of these patients (7.5%) were diagnosed to have intracranial bleed. Recovery was observed in 28 of 35 patients (80%), as five patients went against medical advice. Seven patients died, giving mortality of 20%.

Conclusion: Disease-specific clinical profiles with vigilant monitoring and proactive care is the key for early diagnosis and salvaging these patients. Even rare/uncommon diagnosis should be considered in differentials to avoid delay in management. Reporting of these cases in national data base will increase awareness among physicians, thus decreasing mortality and morbidity.

Key Words: "AUFI "(Acute undifferentiated febrile illness; "MODS"(Multi organ dysfunction syndrome).

Introduction

Fever is a common presenting complaint in the developing world and is the most common presentation in most of the healthcare delivery systems in India. Febrile illness can be localized to organ systems or non localized, commonly referred to as acute undifferentiated febrile illness (AUFI). However, in the developing world, the self limiting fever is no more restricted to general wards and clinics.

There has been a recent surge in patients presenting to critical care units with AUFI rapidly progressing to multi organ dysfunction syndrome (MODS). India, being a tropical nation, is a fertile nest for potentially lethal illnesses such as malaria, dengue fever, enteric fever, leptospirosis, rickettsiosis and influenza A.[1] There is a paucity of literature on the appropriate evaluation, presentation and outcomes of adult fever patients progressively worsening on a short notice in our ICU's. [2]

In the absence of established protocols, patients may be subjected to unnecessary investigations at considerable cost and the inappropriate prescribing of antimicrobial therapy. [3]

Objective

The aim was to study the presentation, epidemiological shifts, complications, and outcomes of patients presenting to the critical care unit with fever as their chief complaint with rapid progression to MODS. The accumulation of data on a multicentre basis can standardize the approach to such patients in a way that will reduce unnecessary testing and inappropriate use of antibiotics. In addition aim was to stress on the intensive care with aggressive proactive measures which can improve the mortality data of any critical care unit.

Study Design

Detailed history was recorded and detailed clinical examination was done in all the patients who presented with fever and MODS. Investigations done included: hemogram, metabolic profile, chest radiography, and electrocardiogram. Peripheral smear for malarial parasite was examined in all the patients. Samples for blood cultures and urine cultures were collected and any clinically obvious site of sepsis was investigated. Most of these patients underwent computed tomography (CT) of the thorax. Serological tests for other etiologies like influenza, dengue, scrub typhus and leptospirosis were also done.

Methods

All patients between 14 and 70 years of age, admitted to the Department of Critical Care, Fortis Hospital, Mohali who had had a febrile illness for 5-21 days, with no evident focus of infection following initial clinical evaluation and who required hospitalization, were enrolled into the study. Patients were excluded if they declined to participate in the study.

Results

From July 2012 to October 2012, 40 patients were enrolled. All patients enrolled met the criteria of fever (> 38.0°C). The mean age of enrolled patients was 44.5 years (interquartile range [IQR] 22-67 years of age) (Fig.1) and males (65%) outnumbered females (35%) (Fig.2).

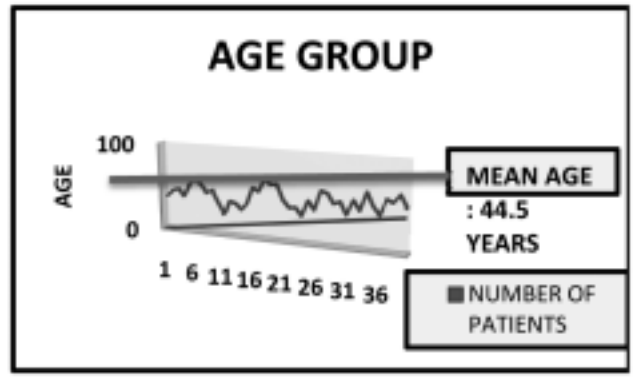


Fig.1 Mean age of the enrolled patients

Fig.2 Sex distribution of the study group

The patients came from the northern Indian states of Punjab (60.5%), Haryana (31.8%) and Himachal Pradesh (7.7%). There was no correlation with common sources like working in farm lands, contact with animals and other epidemiological risk factors.

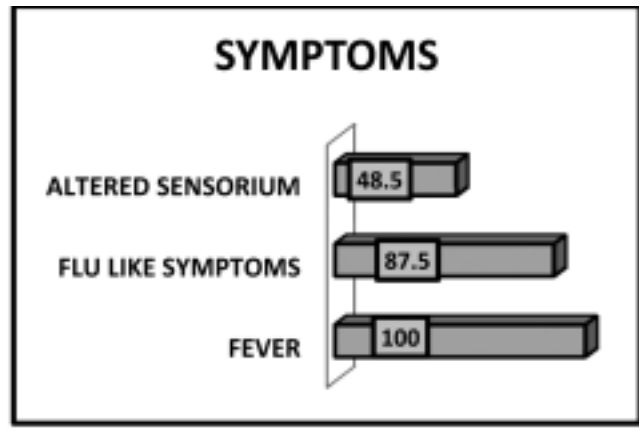


Fig.3 Symptoms on presentation to ICU

AFI predominantly occurred during the monsoon and subsequent months between July to October. The mean time from onset of symptoms to presentation was 9.7 days. The most common symptoms reported by enrolled patients included fever (100%), flu like symptoms (87.5%) and altered sensorium (48.5%) (Fig 3).

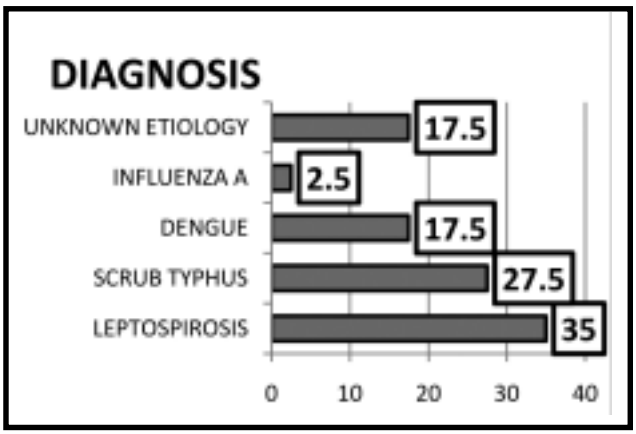


Fig.4 Distribution as per diagnosis

Laboratory testing was performed for agents believed to be endemic to the region in addition to a variety of emerging pathogens. The final diagnosis were leptospirosis (35%), Scrub typhus (27.5%), Dengue (17.5%), Influenza A (2.5%) and unknown etiology (17.5%) (Fig.4). All of these patients deteriorated and developed MODS. Respiratory complications were most common in our study (100%). Several cases presented with severe icteric disease and renal failure (74.5% & 60.5% respectively). Coagulation disorders (84%) especially thrombocytopenia was common.

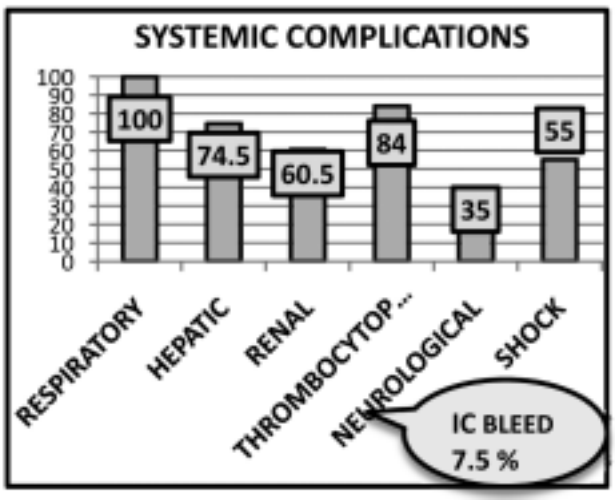


Fig.5 Systemic complication during ICU stay

Neurological manifestations were seen in 35% of our cases, three of these patients (7.5%) were diagnosed to have intracranial bleed. 55% cases were in shock during some point of time in their ICU course (Fig 5).

Outcome analysis revealed complete recovery in 28 of 35 patients (80%). However five patients left against medical advice (LAMA) and hence outcome could not be assessed in them. Seven patients died, giving a mortality rate of 20% in the remaining 35patients.(Fig.6)

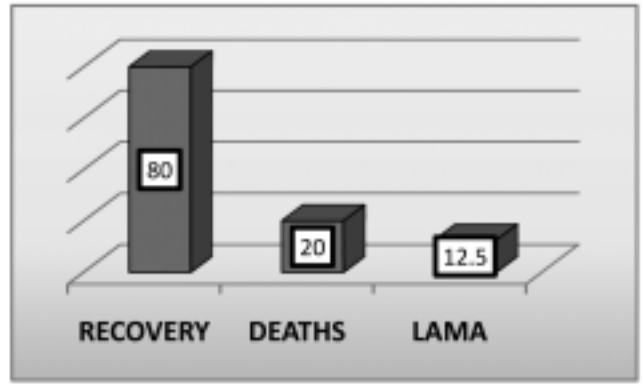


Fig.6 Outcome analysis

Discussion

The agents of human febrile illness can vary by region and country suggesting that diagnosis, treatment, and control programs need to be based on a methodical evaluation of area-specific etiologies. Limited resources and the great diversity of acute febrile illness (AFI) etiologies in India challenge diagnosis, treatment, and public health responses to endemic and epidemic diseases. Further confounding this is the fact that a majority of the patients present with non-descript symptoms (e.g., low-grade fever, general malaise, headache, and muscle ache) and usually no focal point of infection initially but deteriorate rapidly. Health care providers lacking proper knowledge are usually unable to determine specific etiologies, seriousness and often lead to misuse of useful diagnostic tests and antibiotics. In this study, we identified influenza, leptospira, dengue and scrub typhus as the most frequently identified pathogens associated with AFI. Although recently leptospirosis is being increasingly reported from the north Indian subcontinent, the actual incidence is unknown.[4] Our study showed a high scrub typhus and dengue proportion, probably due to low disease awareness and, consequently,

a higher referral rate. Dengue fever incidence has been estimated at 14% among AFIs in a rural population-based southern Indian study and 48% in a hospital-based study in urban northern India. [3]

Respiratory disease

Respiratory symptoms, signs and abnormal chest radiography were the most common manifestation in our study group. Pulmonary involvement, commonly interstitial pneumonitis with possible vasculitis, leading to acute respiratory distress syndrome (ARDS), was reported in up to 55% of scrub typhus patients.[5] A much higher incidence of ARDS in scrub typhus was documented in our cohort. Influenza associated ARDS is documented in 2.1-11.4% of Indian in-patients, the risk being higher among pregnant and non-immune individuals.[6]

The pathophysiology of ARDS in dengue is the result of endothelial injury, increased alveolar permeability and fluid overload.

Hepatic and renal disease

Majority of patients had injury to liver sinusoidal epithelial cell resulting in elevations in hepatic transaminase levels (74.5% in our study), with relatively mild elevations in alkaline phosphatase and bilirubin. Hepatic injury in leptospirosis causes marginal rise in hepatic transaminases with significant mixed hyper bilirubinaemia due to intravascular haemolysis, hepatocyte dysfunction and bile stasis. In contrast, studies (including ours) have shown that significantly elevated hepatic transaminase levels are common in dengue infections. Normal serum aspartate transaminase (AST) levels are a strong negative predictor for dengue haemorrhagic fever (DHF).[7] Renal failure was seen in 60.5 % of the study group; most commonly in leptospirosis (33%) followed by scrub typhus (16%), dengue (11.9%) and Influenza A (5.6%).

Haematological involvement

Most common hematological abnormality was in the form of thrombocytopenia (80%). Thrombocytopenia was known as integral to the presentation of dengue, with up to 70% of patients with dengue exhibiting this.[8] Marked thrombocytopenia, overt bleeding and haemo concentration secondary to plasma leak favors DHF/dengue shock syndrome (DSS). But in our study leptospirosis (56%), Scrub typhus (38%) and influenza A (13.8%) were also major contributors. Thrombocytopenia in scrub typhus is generally mild.

Central nervous system (CNS) and cardiovascular system (CVS) involvement

In this study, 55% of patients presented to us with shock which was refractory in a few (11%). Though neurological involvement was the least common presentation, altered sensorium, including coma, mainly occurred in scrub typhus (53.6%). Most common presentation in our study was in the form of intracranial bleed. CNS involvement, commonly encephalitis presenting with altered sensorium and seizures, was uncommon in our cohort.

Conclusion

Disease-specific clinical profiles provide a useful methodology to systematically identify and document causes of acute fever. Clinical manifestations and laboratory abnormalities were inconstant; severe complicated disease with respiratory failure, severe hepatic dysfunction, and renal failure was also observed. The increased awareness among physicians of protean clinical manifestations of AUFI and early laboratory diagnosis will help reduce morbidity and mortality associated with disease. It is imperative to maintain a sound epidemiological database of AUFIs. Region-specific epidemiological databases of AFI need to be created so that evidence-based diagnostic criteria and treatment guidelines can be developed.

References

1. Chrispal A, et al: Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. Trop Doct 2010, 40(4):230-4.
2. Gur H, Aviram R, Or J, Sidi Y: Unexplained fever in the ED: analysis of 139 patients. Am J Emerg Med 2003, 21(3):230-5.
3. Joshi R, Colford JM Jr, Reingold AL, Kalantri S: Nonmalarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. Am J Trop Med Hyg 2008, 78(3):393-9.

4. Sethi S, Sharma N, Kakkar N, Taneja J, Chatterjee SS, et al. (2010) Increasing Trends of Leptospirosis in Northern India: A Clinico-Epidemiological Study. PLoS Negl Trop Dis 4(1): e579.
5. Tsay RW, Chang FY. Acute respiratory distress syndrome in scrub typhus. Q J Med 2002;95:126-8.
6. Mohan A, Sharma SK, Bollineni S. Acute lung injury and acute respiratory distress syndrome in malaria. J Vector Borne Dis 2008;45:179-93.
7. Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue illness. J Infect Dis 1997;176:313-21.
8. Memon AR, Afsar S. Thrombocytopenia in hospitalized Dengue patients. Pak J Med Sci 2006;22:141-3.

Radiology pearl

Progressive massive fibrosis

Ruchi Dua

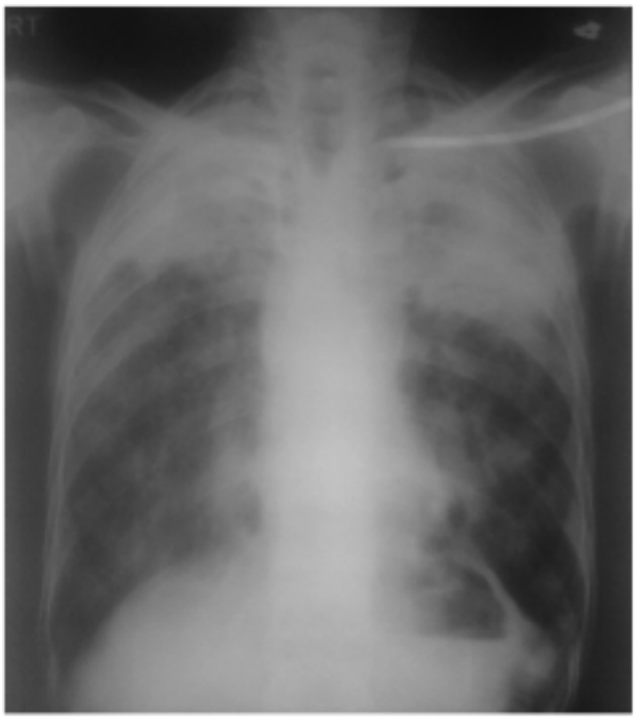
Assistant professor, Dept of Pulmonary Medicine, AIIMS Rishikesh, Uttarakhand, India

Correspondence: Dr. Ruchi Dua,
Assistant professor, Dept of Pulmonary Medicine, AIIMS Rishikesh, Uttarakhand, India
Phone: 9410540684/7895973469
e-mail:vivekvijjan@yahoo.com /doonchestdoctor@gmail.com

.

Clinical Presentation

A 40 year old male presented with cough, expectoration and dyspnea (grade 2 MMRC) over last several years. There was no history of fever or loss of appetite .General examination was unremarkable. Respiratory examination revealed bilateral diffuse rhonchi on auscultation. Chest X ray showed rounded mass opacities in bilateral upper zone and sequential x rays showed a static course. He was on antitubercular treatment for more than one year without clinicoradiological improvement. His sputum was repeatedly negative for AFB and was referred as a case of suspected drug resistant tuberculosis.



What is the diagnosis?

Add to this his occupational exposure history - he had worked in a stone crushing unit for almost 10 years and had stopped working a few years back when his complaints started. In view of definite occupational exposure and suggestive radiological picture he was diagnosed as a case of silicosis(complicated)

Discussion

Failure to respond to antitubercular treatment both clinically and radiologically should not only prompt consideration of drug resistance or noncompliance to treatment but also reconsideration of diagnosis especially if microbiological evidence is lacking. Inadequate response to treatment on the background of co-morbidities like diabetes mellitus and human immunodeficiency syndrome must also be kept a possibility.

Progressive massive fibrosis (PMF) refers to the formation of large conglomerate mass like lesions with irregular margins predominantly in the upper lobes. Though classically described in the context of pneumoconiosis like Coal worker's pneumoconiosis and silicosis, it has occasionally been described with talcosis[1], berylliosis[1] kaolin pneumoconiosis[2] and pneumoconiosis from carbon compounds,[2] such as carbon black, graphite, and oil shale. Conglomerate masses can also develop in Sarcoidosis[3].The diagnosis of PMF requires the presence of a large opacity exceeding 1 cm (on Chest x-ray). PMF can be mistaken for bronchogenic carcinoma and vice versa. PMF lesions tend to grow very slowly, so any rapid change in size or

development of cavitations, should prompt a search for either alternative cause or secondary disease. Carcinoma and tuberculosis are two potential complications. The large opacities gradually migrate toward the hilum, leaving emphysematous lung tissue between the fibrotic tissue and the pleural surface. Treatment is conservative with avoidance of further exposure but it is usually progressive even after cessation of exposure. The diagnosis of pneumoconiosis relies heavily on a proper meticulous history and is one of the DPLDs where only history is rewarding in making a proper diagnosis.

Reference

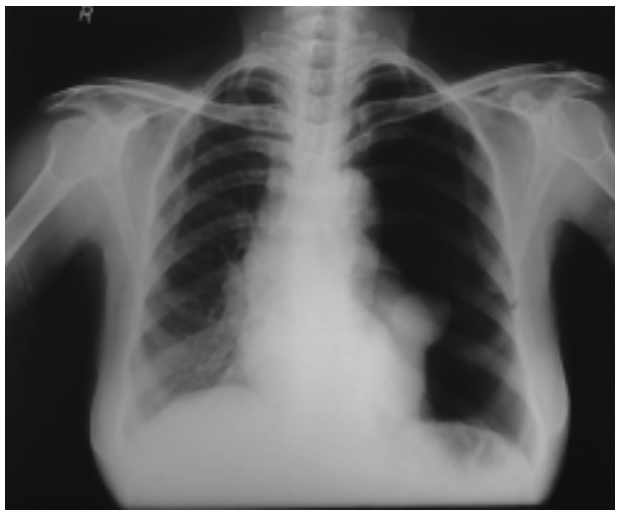
1. Chong S et al. Pneumoconiosis: Comparison of Imaging and Pathologic Findings. RadioGraphics, 2006; 26:59-77.
2. Glazer CS and Newman LS. Occupational Interstitial Lung Disease. Clinics Chest Med, 2004; 25:467-478.
3. Pipavath S and Godwin JD. Imaging of Interstitial Lung Disease. Clinics Chest Med, 2004; 25:455-465.

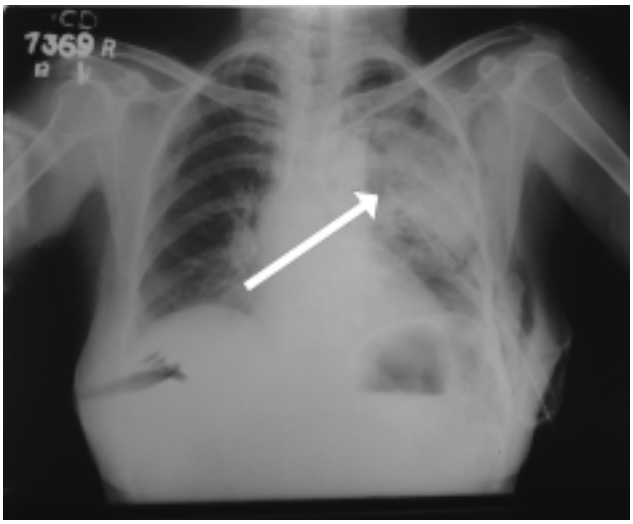
Radiology Quiz

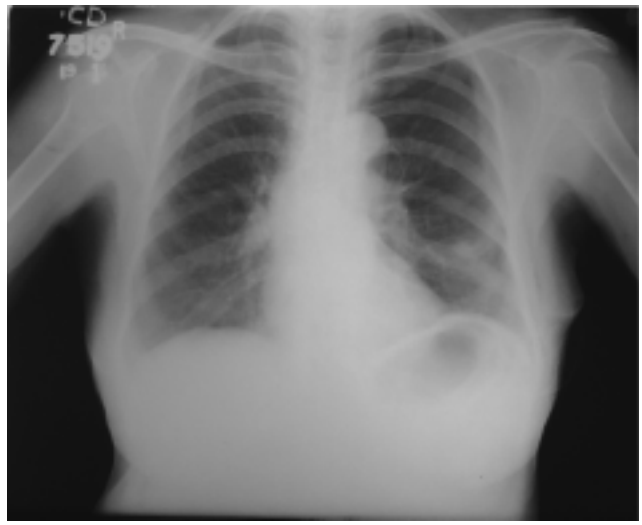
***Sunny George, *Anandan.P.T, **P.T.James**

*Associate Professor , * * Professor
Dept.of.Pulmonary Medicine, Govt.Medical College, Kozhikode.

Correspondences: Dr. Sunny George
Associate Professor, Department of Pulmonary Medicine,
Government Medical College, Kozhikode. sunsuna1@gmail.com







The most likely reason for the non homogenous opacity seen on the left side lung field(bold white arrow) in the second Chest X-ray in an elderly female admitted with left sided acute chest pain which got cleared (3rd Chest X-ray) with supportive management and high flow oxygen.

Interactive Case Discussion

Elderly man with Hemoptysis

Vishnu Sharma M*,Anupama N **, Harsha D.S *, Rahul Antony Simon******

* Professor and Head, Dept of Pulmonary Medicine, A J Institute of Medical Sciences, Mangalore, Karnataka. ** Department of Physiology, Kasturba Medical College, Manipal University, Mangalore, Karnataka, India *** Assistant Professor, Dept of Pulmonary Medicine, **** Postgraduate, Dept of Pulmonary Medicine, A J Institute of Medical Sciences, Mangalore, Karnataka.

Correspondence: Dr Vishnu Sharma
Professor and Head, Dept of Pulmonary Medicine, A J Institute of Medical Sciences, Mangalore, Karnataka.
Mail Id: drvishnusharmag@gmail.com

.

A 76 year old man was admitted to our hospital with history of recurrent mild hemoptysis associated with cough for last 6 months. He also had gradual onset of hoarseness of voice for last 3 months. He had no throat pain, stridor or nasal symptoms. He did not give any history of breathlessness, fever, cough, sputum, chest pain or weight loss. He had no cardiac or gastro intestinal symptoms. He had no past history of hemoptysis, pulmonary tuberculosis, asthma or chronic obstructive pulmonary disease (COPD). He never smoked. He was diagnosed to have Rheumatoid arthritis 25 years back but was not on treatment. He had no symptoms of active Rheumatoid arthritis.

Question 1. Which of the following is least likely diagnosis in this patient? (Select any two options)

A Pulmonary Tuberculosis

B Bronchogenic carcinoma

C Bronchiectasis

D Rheumatoid Interstitial Lung Disease (ILD)

E Laryngeal carcinoma

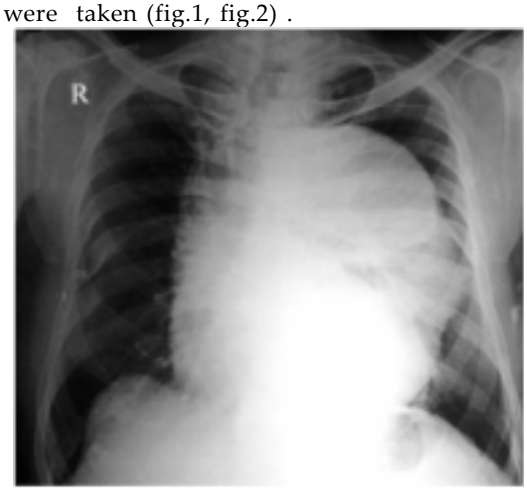
Answer: D and E

Pulmonary tuberculosis, bronchogenic carcinoma and bronchiectasis can present with the above symptoms. Recurrent Hemoptysis may be the sole symptom of pulmonary TB and bronchogenic carcinoma. Bronchiectasis of upper lobe can present with hemoptysis as the only symptom.

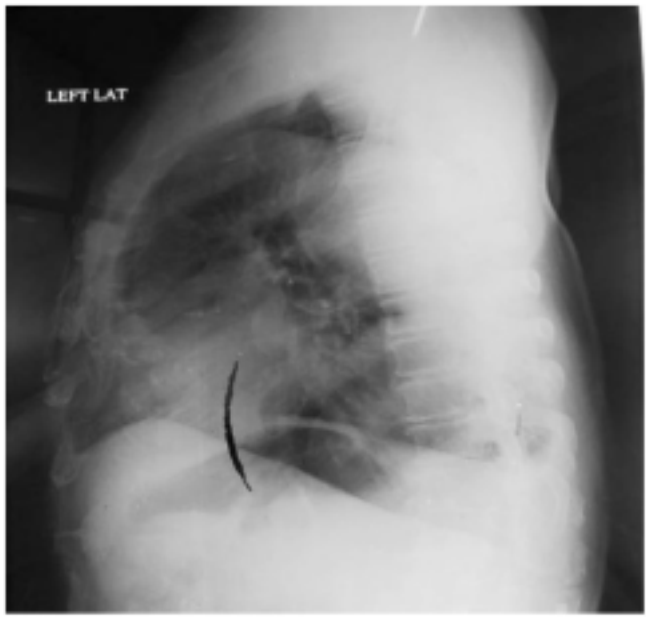
Hemoptysis as the only symptom in rheumatoid ILD and Laryngeal carcinoma is unlikely. Breathlessness is an essential symptom in rheumatoid ILD. Patients with laryngeal carcinoma develop early stridor and in them hemoptysis is unusual.

Physical examination

He had mild joint deformities due to rheumatoid arthritis. There were no signs or symptoms of active rheumatoid arthritis. He had no clubbing, lymphadenopathy or pallor. ENT examination revealed immobile left vocal cord. Respiratory system examination showed impaired percussion note in left infra clavicular area with slight decrease in the intensity of breath sounds. Cardiovascular system examination was normal. All peripheral pulses were felt. X-ray chest PA and left lateral view were taken (fig.1, fig.2) .



(Fig.1)



(Fig.2)

Question 2: What is the diagnosis from chest x-ray?

A Bronchogenic carcinoma

B Thymoma

C Intra thoracic goiter

D Lymphoma

E Fusiform Aortic aneurysm

Answer: E

Chest x ray shows a smooth well circumscribed opacity with smooth borders and in the lateral view it is clearly seen as dilatation of the lower part of arch and descending aorta which is diagnostic of aortic aneurysm.

Question 3: Which is a rare symptom in thoracic aortic aneurysm?

A Pressure symptoms

B Chronic cough

C Hemoptysis

D Chest pain

E Congestive cardiac failure

Answer: C

Hemoptysis is a rare symptom in thoracic aortic aneurysm. Most common symptom is vague non specific chest pain due pressure on adjacent structures. Chronic cough is due to pressure on airways. Compression of adjacent structures by aortic aneurysm can lead to hoarseness of voice, dysphagia, raised left dome and dyspnea. Superior venacava (SVC) obstruction and congestive cardiac failure can occur in ascending aortic aneurysm.

Question 4: Which of the following is the most important cause for descending thoracic aortic aneurysm?

A Cystic medial degeneration

B Marfan's syndrome

C Family history of thoracic aortic aneurysm

D Atherosclerosis

E Syphilis

Answer: D

All the other are causes for ascending aortic aneurysm.

Question 5: Which is a wrong statement?

A Larger the size greater the chance for rupture in aortic aneurysm

B Thoracic aortic aneurysm is more common than abdominal aortic aneurysm

C Descending thoracic aorta is the most common location of a thoracic aneurysm

D Aortic aneurysm is more common in elderly males

E Smokers have higher risk to develop aneurysm

Answer: B

Most common site for aortic aneurysm is abdominal aorta below the level of renal arteries. All patients diagnosed to have thoracic aortic aneurysm should undergo ultrasound examination of abdomen as sometimes they may have co-existent abdominal aortic aneurysm. Smoking, atherosclerosis and age are the most important risk factors to develop aortic aneurysm.

Question 6: Which is not a risk factor for aortic aneurysm?

A Infection

B Trauma

C Pulmonary Tuberculosis

D History of coronary artery disease

E Family history of aortic aneurysm

Answer: C

Pulmonary TB does not predispose to the development of aortic aneurysm

Further investigations

Blood routine investigations were normal. Sputum for AFB smear was negative. Serological tests for syphilis were negative. Rheumatoid factor was positive.

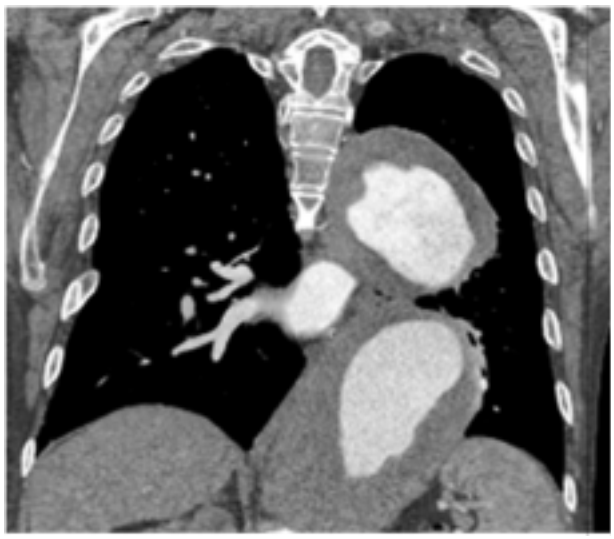
Question 7: What is the next diagnostic investigation?

A Thoracic CT angiogram
B Aortogram
C Echocardiography
D Pulmonary angiogram
E CECT thorax

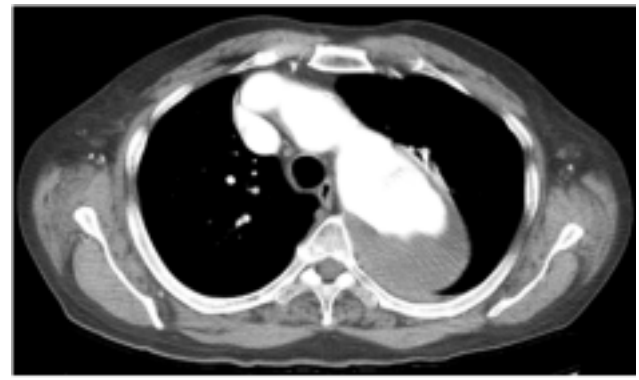
Answer: A

The diagnostic investigation in thoracic aortic aneurysm is thoracic CT angiogram although other investigations are also useful.

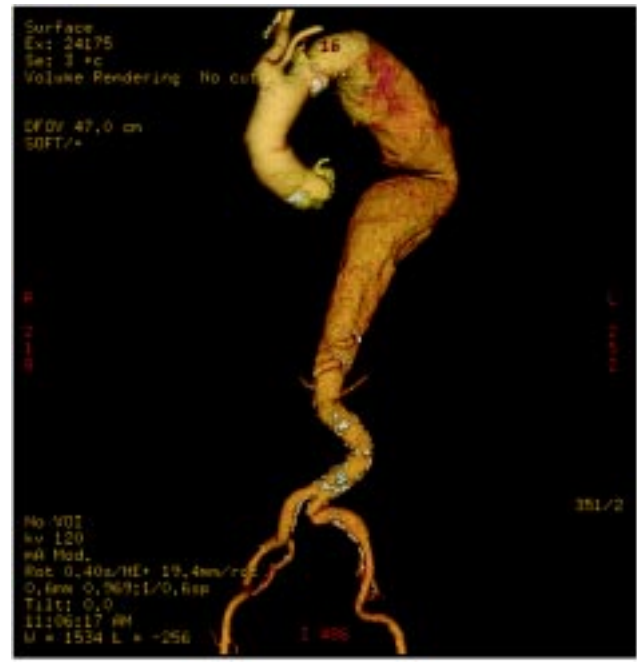
CT angiography showed (fig. 3,4,5) fusiform aneurysmal dilatation of the distal arch of aorta, descending thoracic aorta and abdominal aorta till the level of left renal arteries. Eccentric thrombus was seen in the distal arch of aorta and proximal descending thoracic aorta. Concentric thrombus was seen in the distal descending thoracic aorta and the suprarenal abdominal aorta. There was no evidence of dissection/peri aneurysmal leak or hematoma. There was no lung lesion or mediastinal adenopathy.



(fig.3)



(fig.4)



(fig.5)

Question 8: What is the most likely cause for hemoptysis in aortic aneurysm in this patient?

Answer: Leaking aneurysm (Aorto-bronchial fistula)

Aorto-bronchial fistula is a rare but dreaded complication of aortic aneurysm and is the cause for recurrent hemoptysis in these patients. It can lead to sudden death due to massive bleed. Bronchoscopy is contra indicated in these patients as it may lead to aortic rupture if the aneurysm is compressing the airways.

Question 9: Which of the following is not considered during plan for surgery in aortic aneurysm?

A Size greater than 5.5 to 6 centimeters
B Absence of symptoms
C Aneurysm growth rate 0.5 centimeters over a period

of six months to one year

D Presence of genetic disorders or familial history of thoracic aneurysms

E Patient's ability to tolerate the procedure

Answer: B

A large aneurysm should be treated by surgery even in the absence of symptoms as risk of rupture increases with size and rapidity of increase in size. All patients with symptomatic aneurysms also should be treated surgically irrespective of the size of the aneurysm.

Question 10: Which is a wrong statement regarding Aortic aneurysm due to rheumatoid arthritis?

A Occurs due to rheumatoid vasculitis.

B It is rare

C These patients high titers of rheumatoid factor

D Usually affects descending aorta.

E These patients usually have severe rheumatoid arthritis.

Answer: D

It usually affects ascending aorta.

Due to age, poor general condition and large size of the aneurysm extending from distal arch of aorta to the level of left renal arteries surgery was not done, as operative risk was high.Medical management of aortic aneurysm includes control of hypertension if patient is hypertensive and regular follow up to monitor the rate of increase in size of the aneurysm.

Final call came one evening. He was rushed to hospital with massive hemoptysis but breathed his last before he could reach the hospital.

Learning points

Aortic aneurysm can present with a variety of respiratory symptoms. When there is a benign looking mass in chest x-ray on the left side consider aortic aneurysm as one of the differential diagnosis. Definitive treatment for aortic aneurysm is surgery.

References:

1. Aneurysm. National Heart, Lung and Blood Institute. http://www.nhlbi.nih.gov.
2. Hiratzka LF, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive summary. Journal of the American College of Cardiology. 2010;55:27.
3. Aortic aneurysms. The Society of Thoracic Surgeons. http://www.sts.org/patient-information/aneurysm-surgery/aortic-aneurysms.
4. Marfan syndrome. National Heart, Lung and Blood Institute. http://www.nhlbi.nih.gov/health.
5. Booher AM, et al. Diagnosis and management issues in thoracic aortic aneurysm. American Heart Journal. 2011;162:38.
6. Jondeau G, et al. Genetics of thoracic aortic aneurysms. Current Atherosclerosis Report. 2012;14:219.
7. Shah AA, et al. Results of thoracic endovascular aortic repair 6 years after United States Food and Drug Administration approval. Annals of Thoracic Surgery. 2012;94:1394.
8. Grogan M (expert opinion). Mayo Clinic, Rochester, Minn. Feb. 18, 2013.

Case Report

Solitary plasmacytoma with secondary amyloidosis

Sisira M *, Sunny George, Anandan P T**, James P T*****
*Senior Resident, ** Associate Professor, ***Professor
Department of Pulmonary Medicine, Govt. Medical College, Kozhikode.

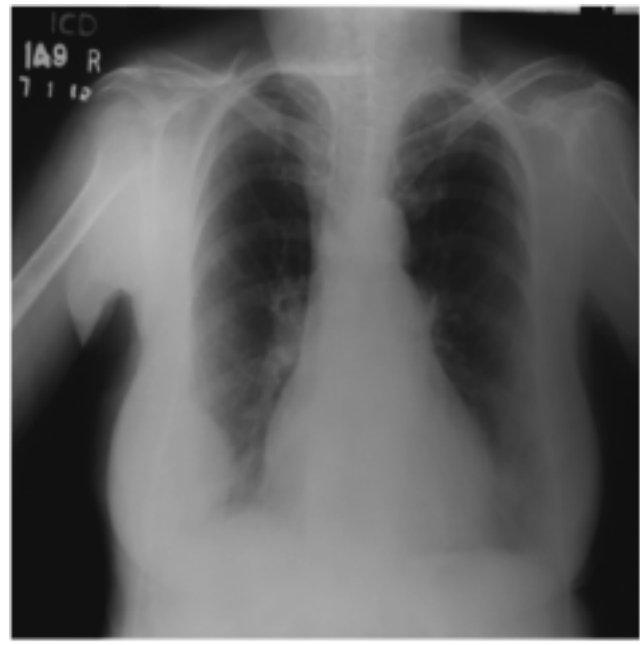
Abstract

Solitary plasmacytoma is a localized lesion and extremely rare amongst the plasma cell tumors. Unlike multiple myeloma there is no evidence of disseminated disease. We present the case of a seventy five year old female presenting with chest pain which turned out to be a solitary plasmacytoma of eighth rib on the right side which itself is a rare disease and the histopathology specimen revealed the presence of amyloid material making it all the more interesting as it turned out to be a case of secondary amyloidosis in this rare tumor.

Key words: Solitary plasmacytoma, Secondary amyloidosis

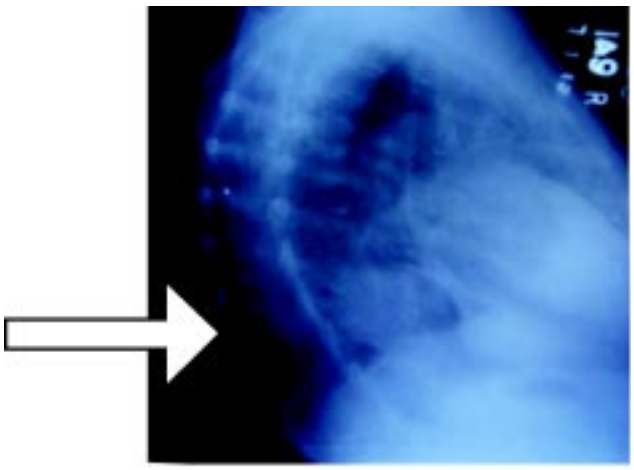
Case report

A seventy five year old female presented to us with right sided chest pain of six months duration and breathlessness of one week duration. The chest pain was more or less localized to the infra axillary area which was a dull aching pain with tenderness on deep palpation. She gave history of MMRC Grade II dyspnea and no wheezing during this episode. She gave history of recurrent episodes of wheezing for the last six years. She also gave history suggestive of rhino bronchial allergy. She was getting regular treatment for moderate persistent asthma for the last two years and was well controlled. She was on treatment for systemic hypertension for the past five years. There was no history of loss of appetite, loss of weight, cough or haemoptysis. She gave history of blunt trauma to chest about five years back. General examination revealed pallor. There was no significant lymph node enlargement. Respiratory system examination showed kyphosis and fullness over the right infra axillary area and tenderness could be elicited. There was impaired resonance in the right infra axillary area with reduced vocal fremitus. Breath sounds and vocal resonance were decreased in the above area. Hence a provisional diagnosis of right lower lobe peripheral mass lesion with possible chest wall involvement in a moderate persistent well controlled asthmatic was made.



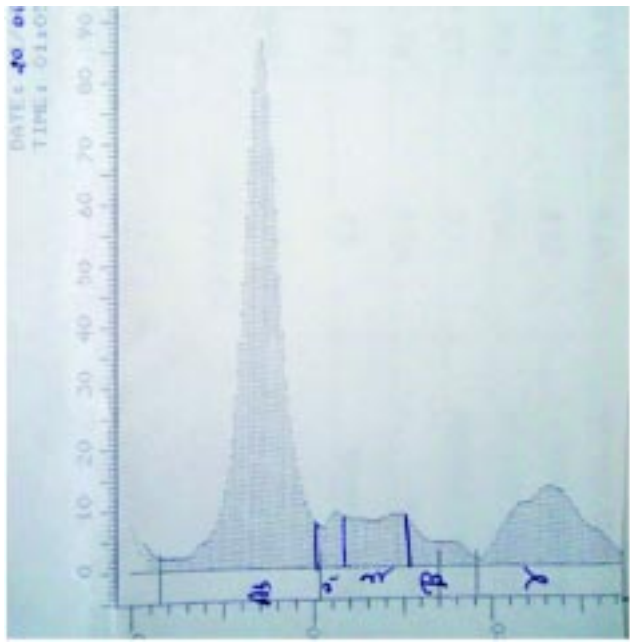
Chest X-ray PA view Fig (1)

Her investigations were as follows; Hb: 10.8gm%, TC- 10400, DC P42 L 39 E19, ESR -40 mm/1st hr, RBS-112mg%, Sputum AFB X 2 samples -negative, Urea - 10mg%, S.creatinine - 0.8.Her liver function tests were normal. Sputum cytology was negative. Mantoux test was non reactive.

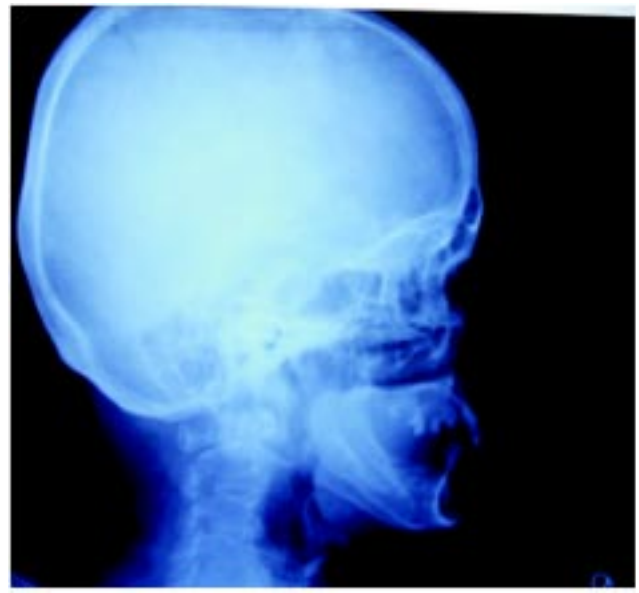


Chest X-ray right lateral view Fig (2)

Her Chest X-ray PA view revealed a well defined opacity involving the right lower zone close to the costophrenic angle with a pleural base and making an obtuse angle with the chest wall which localises the lesion to the extra pleural region fig (1). This mass was clearly made out (bold arrow) in the right lateral projection also fig (2). Hence the differential diagnoses of a pleural based mass lesion, chest wall mass, encysted effusion or a peripheral lung mass with chest wall extension were considered. In view of her high eosinophil count, a peripheral smear was done which revealed normocytic normochromic blood smear with eosinophilia. Her urine Bence jones protein was negative and serum electrophoresis to rule out multiple myeloma did not reveal the presence of M band fig (3).



Serum Electrophoresis fig (3)



X-ray Skull Lateral View fig (4)

Lateral view of her skull did not reveal any punched out lesions. A CT-Chest taken showed an expansile lytic lesion with cortical break and multiple bone fragments associated with intra and extra thoracic soft tissue component involving the anterolateral aspect of 8th rib on the right side and the possibilities considered were metastasis or a lesion confined to rib like tuberculous osteomyelitis or solitary plasmacytoma.fig (5&6)

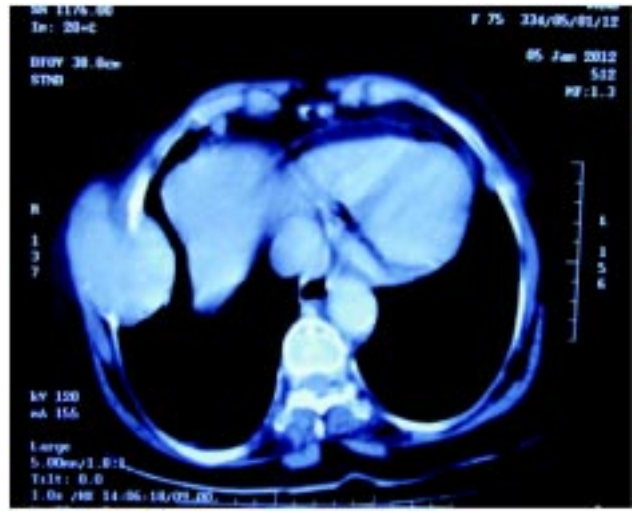


Fig (5)

Fig.5 CT chest mediastinal window showing the peripheral lesion arising from the rib

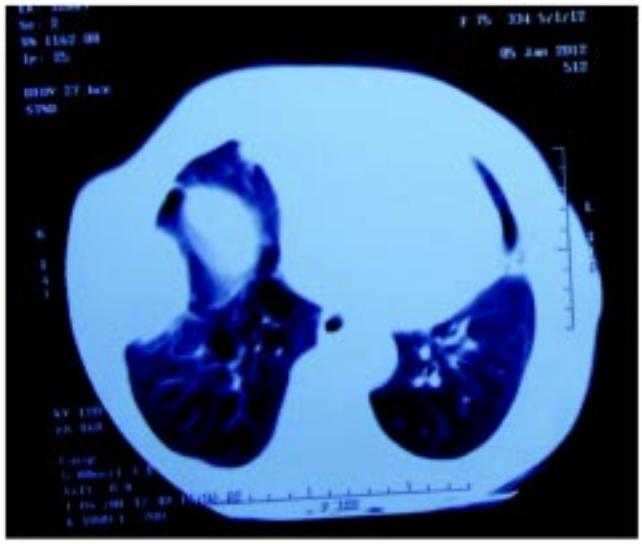


Fig.6 CT chest Lung window showing the peripheral lesion arising from the rib

Hence we proceeded with a Trucut biopsy of the chest wall lesion and a bone marrow study, as we wanted to rule out a plasma cell dyscrasia in this patient fig (3). Bone marrow biopsy showed mild increase in the eosinophilic precursors with 2% plasma cells. Erythroid, myeloid precursors and megakaryocytes were seen normally. Her trucut biopsy specimen yielded sheets of plasma cells infiltrating abundant eosinophilic material which was suggestive of amyloid material. This was hence subjected for immunohistochemical studies and congo red staining which was CD 138 +ve and congo red positive with kappa restriction Fig (7,8,9, 10&11).

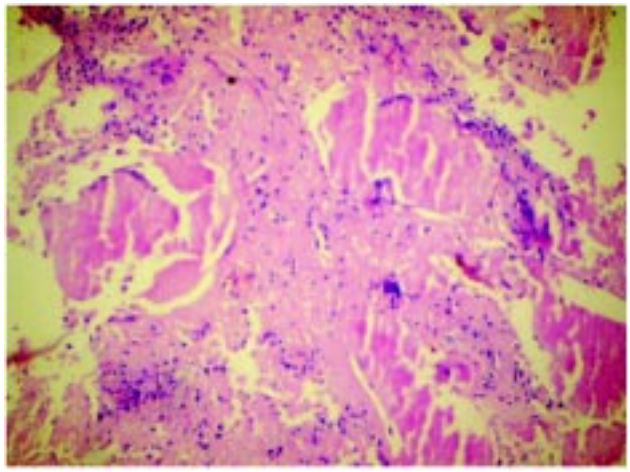


Fig 7

H& E stained Low power view of Trucut specimen showing abundant eosinophilic material

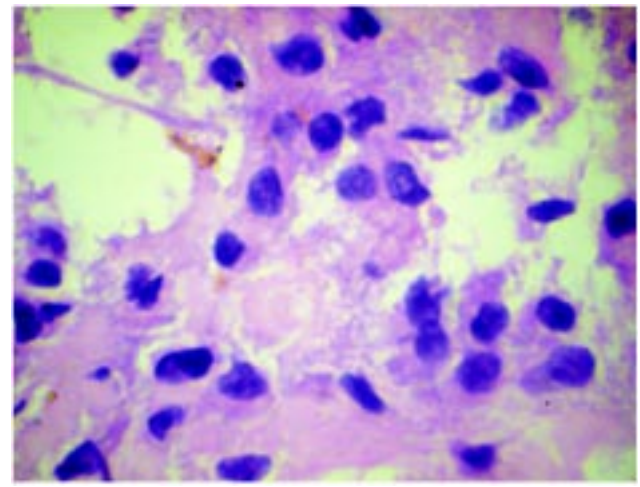


Fig 8

High power view showing sheets of plasma cells in abundant eosinophilic material

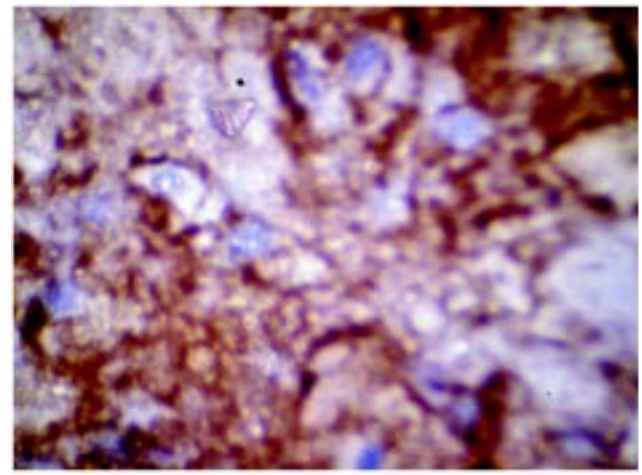


Fig 9

Immunohistochemistry (IHC) staining with CD138

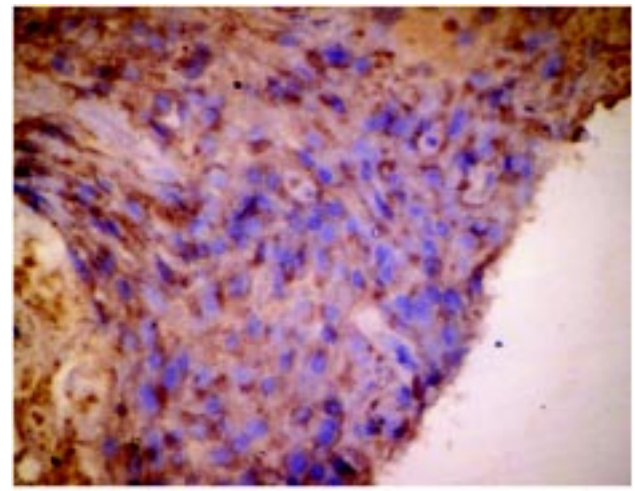


Fig 10
IHC showing kappa restriction

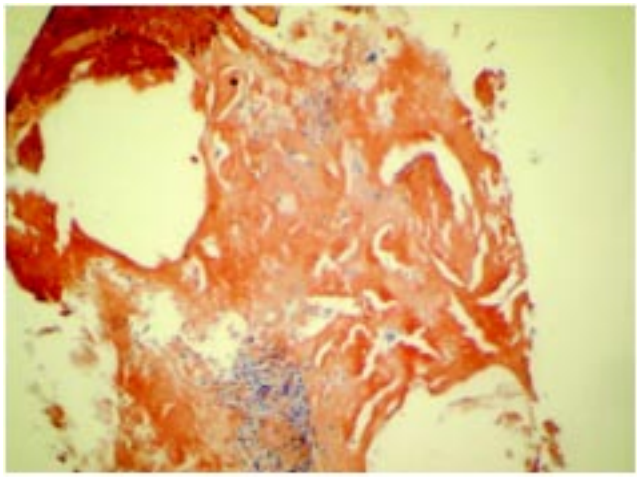


Fig 11

Congo red staining shows brisk uptake

Hence a diagnosis of solitary plasmacytoma of the right eighth rib with secondary amyloidosis was made. She was advised local radiotherapy and limited resection. The patient however was not willing for further management and opted for palliative care.

Discussion

Solitary plasmacytoma of bone (SPB) is a rare localized lesion that accounts for only 4% of all malignant plasma cell tumors. It is relatively benign plasma cell proliferative disorder with monoclonal plasma cell proliferation[1]. Myeloma on the other hand is a clonal haematopathy. Plasmacytomas can be divided into multiple, solitary osseous, and solitary extraosseous or extramedullary plasmacytomas[2] .The incidence of SPB has been reported to be 3/10 00 000 annually. The average age on presentation was 59.5 years with a range from 39 to 77 years[4] .It may progress to multiple myeloma in 10% cases.To make a diagnosis of solitary plasmacytoma, there should be: 1)Single area of bone destruction due to clonal plasma cells 2)Bone marrow not consistent with multiple myeloma 3) Normal skeletal survey 4) No end organ damage other than solitary bone lesion[3] . According to the current recommendations, the detection of a monoclonal component in the serum or urine does not exclude a diagnosis of solitary plasmacytoma[4]. CD138 or syndecan 1 positivity of the trucut specimen can be considered as an excellent marker for plasmacytic differentiation[5]. Kappa restriction demonstrated in immunohistochemistry signifies the clonality of light chain present in the lesion[6].Congo red staining with yellow green birefringence under polarized light is the diagnostic technique for demonstrating amyloid material in tissue specimen and our specimen was proved to have amyloid deposits which is hence secondary amyloidosis in a SPB[7]. Treatment is by preoperative radiotherapy with complete en-block resection, followed by adjuvant chemotherapy. Radiation therapy was used as the primary treatment for solitary plasmacytoma. Aviles et al, observed that most patients treated with adequate radiation therapy alone will develop multiple myeloma within the first 3 years after diagnosis and treatment. Low doses of melphalan and prednisolone contributed to an improvement in disease-free survival and overall survival in patients with SPB, compared with patients who were treated with radiotherapy alone. Hence preoperative radiotherapy with complete en-block resection, followed by adjuvant chemotherapy, is the currently accepted best treatment strategy for SPB.

References

1. Joshi A, Jiang D, Singh P and Moffat D: Skull base presentation of multiple myeloma. Ear Nose Throat J.90:E6-E9. 2011.
2. Ashiq Masood, Hudhud Kanan H, Hegazi AZ, Syed Gaffar. Mediastinal plasmacytoma with multiple myeloma presenting as a diagnostic dilemma. Cases J. 2008; 1:116.
3. International Myeloma Working Group: Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol.121:749-757. 2003.
4. Ooi GC, Chim JC, Au WY, Khong PL. Radiologic Manifestations of Primary Solitary Extramedullary and Multiple Solitary Plasmacytomas. AJR Am J Roentgenol. 2006;186:821-7.
5. Chilosi M, Adami F, Lestani M, Montagna L, Cimarosto L, Semenzato G, Pizzolo G, Menestrina F. CD138/ syndecan-1: a useful immunohistochemical marker of normal and neoplastic plasma cells on routine trephine bone marrow biopsies.Mod Pathol. 1999 Dec; 12(12):1101-6.
6. Meis JM, Butler JJ, Osborne BM, Ordóñez NG.Solitary plasmacytomas of bone and extramedullary plasmacytomas. A clinicopathologic and immunohistochemical study. Cancer. 1987 Apr 15; 59(8):1475-85.
7. Khurana R, Uversky VN, Nielsen L, Fink AL.Is Congo red an amyloid-specific dye? J Biol Chem. 2001 Jun 22 ;276(25):22715-21. Epub 2001 Feb 28 .

Case Report

Where the mind knows, the eyes see- Dyskeratosis Congenita, A Genetic ILD.

Neethu K Kumar*, Kiran VN Jyothi E***, Suraj KP******

*Junior Resident, **Assistant Professor,
*** Associate Professor, ******Additional Professor. Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode.

Correspondence: Dr. Suraj KP, Additional Professor,
Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode. E Mail - drsurajkp@yahoo.com

Abstract

Interstitial lung disease with specific phenotypic clues should be interpreted by the astute clinician to make a proper diagnosis. Dyskeratosis congenita is a progressive, multisystem, inherited disorder of telomere biology with high risk of morbidity and mortality from bone marrow failure, hematologic malignancy, solid tumors, and pulmonary fibrosis. Here we report a case of dyskeratosis congenita with interstitial lung disease.

Key Words - Dyskeratosis congenita, interstitial lung disease (ILD), genetic ILD

Case report.

A thirty four year old male school teacher, non-smoker, non alcoholic, presented to us with fever, cough, and progressive dyspnea on exertion of 3 months duration. His symptoms first developed as low grade fever followed by cough associated with occasional scanty mucoid expectoration. There was insidious onset of dyspnea on exertion which progressed from grade 0 (mMRC scale) to grade II in 2 months and grade IV in last 1 month. There was no history of orthopnea, paroxysmal nocturnal dyspnoea, chest pain, hemoptysis, dysphagia or hoarseness of voice. There was no previous history of hypertension, diabetes mellitus or coronary artery disease. He had no exposure to occupational noxious gas, chemical fumes, organic dusts, pet animals or birds. There was no history of any significant drug intake.

He was tall, lean built and poorly nourished with premature greying of hair and alopecia. The striking features on inspection were generalised hypo pigmented and hyper pigmented macules on the face, trunk and limbs and the proliferative lesion on left eye (Fig 1). He had progressive loss of vision of left eye over the last 20 years and it showed features of severe dry eye with keratinisation and symblepharon. There were multiple hyper pigmented macules and patches in the oral mucosa and dystrophic nails. The respiratory system examination revealed bilateral fine end inspiratory crepitations. The heart sounds were normal without any murmurs. His pulse rate and blood pressure were normal and he was tachypneic.

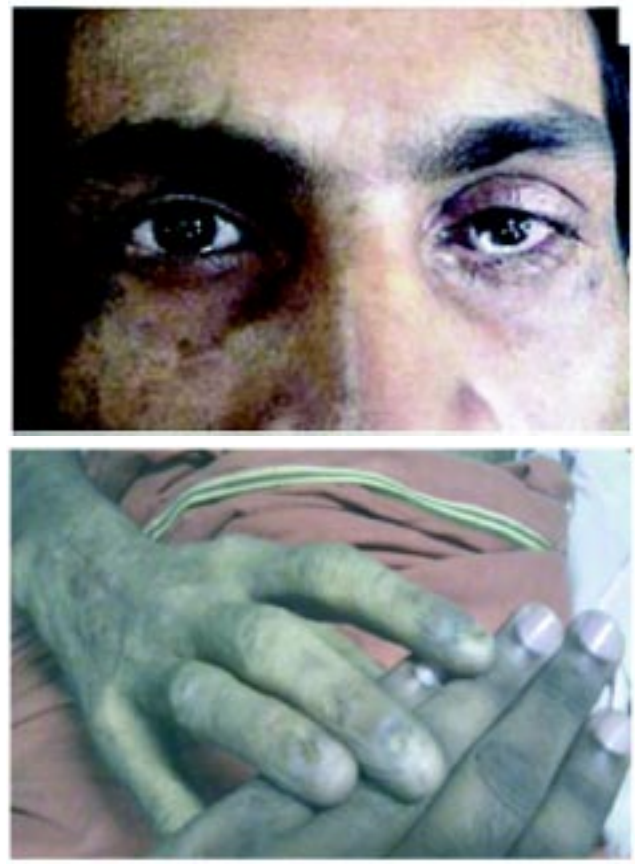


Figure1 : (A) Pigmentation of skin and ocular lesion, (B) Nail changes (compared with normal fingers).

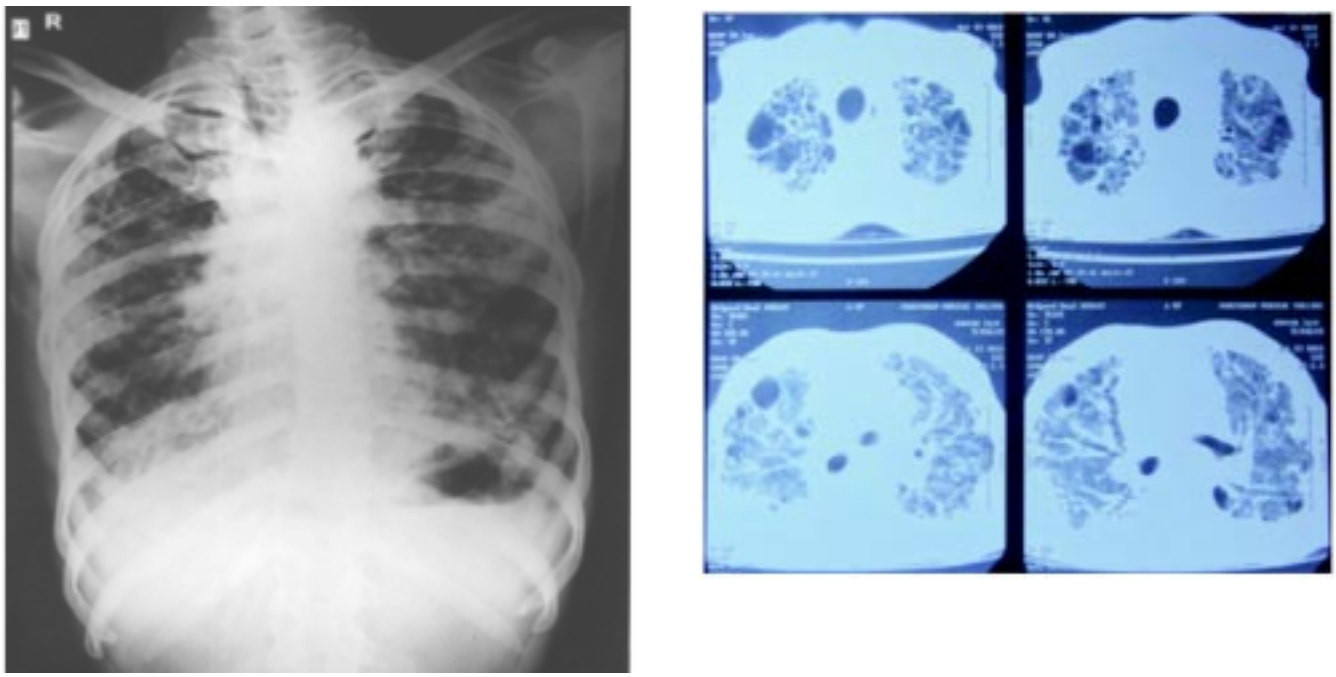


Figure 2: (A) Chest X ray , (B) HRCT

The routine blood investigations were within normal limits except for an elevated ESR value of 112 mm/1st hour. Sputum AFB was negative, Mantoux with 5TU nonreactive, and sputum culture yielded normal flora. Screening for viral markers were also negative.

Chest X- ray revealed bilateral reticulonodular infiltrates in both lung fields with evidence of volume loss involving the right lung. The spirometry showed a restrictive pattern with forced vital capacity (FVC) 1.19L (34.5% of predicted value), forced expiratory volume 1 second (FEV1) 1.17L (39.7% of predicted value) and FEV1/ FVC of 97.9.He was not able to perform a DLCO (Diffusion capacity of lung for carbon monoxide). HRCT Thorax showed diffuse interstitial thickening, peribronchovascular thickening, traction bronchiectasis, areas of subpleural honey combing, few cystic lesions, fibrotic strands and pleural thickening (Fig 2).

This constellation of findings led us to the clinical suspicion of Dyskeratosis congenita associated interstitial lung disease. So to confirm the diagnosis, dermatology, ophthalmology and oral medicine consultations were done.On fibreoptic bronchoscopy there were white patches in posterior pharyngeal wall suggestive of leukoplakia and the trachea was congested. A transbronchial lung biopsy was taken from the right middle lobe which revealed interstitial fibrosis with probable usual interstitial pneumonia pattern on histopathology. An open lung biopsy via mini thoracotomy confirmed UIP pattern on histopathology. A Biopsy of the oral mucosa showed leukoplakia. So with the classical triad of mucosal leukoplakia, dystrophic nails, abnormal skin pigmentation along with biopsy proven interstitial lung disease, we confirmed the diagnosis of dyskeratosis congenita associated interstitial lung disease. Subsequently he was started on corticosteroids, N acetyl cysteine and other supportive measures. Although he showed an initial improvement, his course in the hospital over the next month was stormy and he deteriorated rapidly and succumbed to the illness.

Discussion

Dyskeratosis congenita (DC), is a rare inherited multi system disorder of telomere biology characterized by a triad of nail dystrophy, lacy reticular pigmentation, and oral leukoplakia. The prevalence of Classic dyskeratosis congenita is approximately 1/1,000,000 individuals. Patients with DC are at very high risk of bone marrow failure (BMF), malignancies including head and neck or other cancers, leukemia, and myelodysplastic syndromes (MDS).They are also prone to pulmonary fibrosis, liver disease, neurological, ophthalmic, genitourinary, and gastrointestinal abnormalities. The primary causes of death in patients

with dyskeratosis congenita are bone marrow failure(BMF) and immunodeficiency (60-70%), pulmonary complications (10-15%), and malignancy (10%)[1].

Telomeres, which consist of TTAGGG nucleotide repeats and a protein complex at chromosome ends, are essential for chromosome stability[2]. They are generally very short in individuals with DC. Approximately 60% of persons with DC have an identifiable mutation in one of seven genes important in telomere biology. Inheritance of DC may follow X-linked recessive (DKC1 gene), autosomal dominant (TERC, TERT, or TINF2), or autosomal recessive patterns (NOP10, NHP2, TERT, or TCAB1). Hematopoietic stem cell transplantation (HSCT) can correct BMF and other hematologic complications (i.e., MDS or leukemia), but it does not improve other DC-related manifestations.

Classical DC is an inherited BM failure syndrome characterised by the mucocutaneous triad, also called Zinsser- Engman-Cole syndrome. Clinical manifestations in DC often appear during childhood although there is a wide age range. The skin pigmentation and nail changes typically appear first, usually by the age of 10 years. BMF usually develops below the age of 20 years. In some patients BM abnormalities may appear before the mucocutaneous manifestations and can lead to the initial diagnosis of idiopathic aplastic anemia.

Hoyeraal-Hreidarsson syndrome is an atypical form of DC that can present in the neonatal period and infancy. These are severe variant of DC where death from BM failure/ immunodeficiency occurs before the appearance of the diagnostic features of DC.

Management of DC patients requires a multi-disciplinary approach. General measures like avoidance of direct sunlight, abstinence from smoking and alcoholism is imperative. Oxymetholone can produce an improvement in haemopoietic function in many patients. Successful response to hematopoietic growth factors like GM-CSF, G-CSF and erythropoietic growth factors have also been reported. The main treatment for severe BM failure is allogenic haemopoietic stem cell transplantation. For pulmonary fibrosis associated with DC there are case reports of successful bilateral lung transplantation.

References

1. Giri N, Lee R, Faro A, Huddleston CB,White FVet al. Lung transplantation for pulmonary fibrosis in dyskeratosis congenita: Case Report and systematic literature review. BMC Blood Disord. 2011 Jun 15;11:3
2. Heiss NS, Knight SW, Vulliamy TJ, Klauck SM et al. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nat Genet. 1998 May;19(1):32-8.
3. Dokal I and Vulliamy T. Dyskeratosis congenital. Orphanet Encyclopedia. October 2004

Answer

Re expansion pulmonary edema.

The first Chest X-ray PA view clearly shows the presence of a left sided pneumothorax with the collapsed lung assuming a rounded opacity in the left hilar region. The second X-ray shows an ICD in situ on the left side with minimal surgical emphysema and a non homogenous opacity more confluent in the midzone extending from the hilum to the periphery and partly involving the upper and lower lung zones with clear costophrenic and cardiophrenic angles in the almost fully expanded lung. The last X-ray shows total clearance of the shadows in the left lung zones with conservative management which is most likely due to re expansion pulmonary edema.

Re-expansion pulmonary edema is an uncommon complication following drainage of a pneumothorax or pleural effusion. Re-expansion pulmonary edema in many instances is clinically mild as in this case as it was unilateral and hence the reported incidence is 1% in many studies. Increased pulmonary hydrostatic pressure caused by enhanced venous return, pressure-induced mechanical disruption of the alveolar capillaries, decreased levels of functional surfactant are some of the proposed mechanisms.Treatment is generally supportive, ranging from oxygen supplementation to noninvasive and invasive ventilation. Preventive strategies include the use of low negative pressure (< -20 cm H2O) for suctioning and limiting drainage of pleural fluid if patient develops more than minimal cough,dyspnoea,chest tightness or pain.

MID - PULMOCON 2013

Mid term conference of Academy of Pulmonary and Critical Care Medicine (APCCM)

on 15th DECEMBER 2013

At Surya Regency - Malappuram

Organising Secretary

Dr. Abdul Samad

Mob: 9447106699

GUIDELINES FOR AUTHORS

The merit of the publication lies in its quality and content. Contributions are invited on any aspect of Pulmonary and critical care medicine. Articles are accepted on the basis of significance, scientific perfection and practical applicability. Authors are requested to base their papers on the basis of original work carried out by themselves or their groups. Manuscripts should not be submitted to more than one journal at a time.

All articles are subjected to a peer review process. Each article is assessed blindly by one or more referees depending on the manuscript type and comments sent back to the authors for revision as required. The Editor's decision is final on accepting or rejecting an article.

The types of articles published in the journal are as follows

1. Editorials
2. Reports of original research
3. Critical reviews
4. Meta analysis
5. Case reports (series) with discussions
6. Radiology pearls
7. Educational forum
8. Letters to editor

Manuslcripts should be submitted by e-mail or CD in MS Word addressed to,

Dr. Suraj K.P.
The Editor-in-Chief, Pulmon,
Additional Professor, Dept. of Pulmonary Medicine,
Govt. Medical College, Kozhikode, Kerala, 673008.
Ph. 9447445135
E mail: drsurajkp@yahoo.com

Requirements for submission of manuscript

Presentation of manuscripts should conform with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (see Ann Intern Med 1997;126:36-47).

The manuscript should be accompanied by

1. Covering letter
2. Undertaking by authors
3. Copyright transfer agreement form.

Covering Letter

The covering letter should explain why the paper should be published in the Pulmon. One of the authors could be identified as the corresponding author of the paper, who will bear the responsibility of the contents of the paper. The name, address, and telephone number of the corresponding author should be provided for all future communication related with the publication of the article. The letter should give any additional information that may be helpful to the editor, such as the type of article and whether the author(s) would be willing to meet the cost of reproducing color illustrations.

Undertaking by Author(s)

It is necessary that all the authors give an undertaking (in the format specified by the journal) indicating their consent to be co-authors in the sequence indicated on the title page. Each author should give his or her names as well as the address and designation current at the time the work was done, plus a current address for correspondence including telephone and fax numbers and email address. A senior author may sign the Undertaking by Authors for a junior author who has left the institution and whose whereabouts are not known and take the responsibility. (Format for submission of undertaking is provided at the end of the session.)

Copyright Transfer Agreemnet

Author(s) will be asked to sign a transfer of copyright agreement, which recognizes the common interest that both journal and author(s) have in the protection of copyright. It will also allow us to tackle copyright infringements ourselves without having to go back to authors each time. (Format for submission of copyright is provided at the end of the session.)

Manuscript

Manuscripts should be presented in as concise a form as possible, typewritten in double space and numbered consecutively. The contents should be arranged in the following order:

Title page, Abstract, Key words, Introduction, Material & Methods, Results, Discussion, Summary, Acknowledgement and References. Abstract, Tables and legends for Figures should be typed on separate sheets and not in continuation of the main text. *Figures and Photographs should be presented in JPEG or GIF format.*

Title Page

The title page should carry 1) the title of the article, 2) the name by which each author is known, with his or her highest academic degree and institutional affiliation, 3) the name of the department(s) and institution(s) to which the work should be attributed; 4) disclaimers, if any; 5) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; 6) source(s) of support in the form of grants, equipment, drugs, or all of these.

Title of the article should be short, continuous (broken or hyphenated titles are *not* acceptable) and yet sufficiently descriptive and informative so as to be useful in indexing and information retrieval. A short running title not

exceeding 6-7 words to be provided at the foot of the title page.

Abstract

All manuscripts should have a structured abstract (not more than 250 words) with subheadings of Background

& objectives, Methods, Results ,Interpretation and Conclusions.Abstract should be brief and indicate the scope and significant results of the paper. It should only highlight the principal findings and conclusions so that it can be used by abstracting services without modification. Conclusions and recommendations not found in the text of the articles should not be inserted in the abstract. A set of suitable key words arranged alphabetically may be provided.

Introduction

Introduction should be brief and state precisely the scope of the paper. Review of the literature should be restricted to reasons for undertaking the present study and provide only the most essential background.

Material & Methods

The procedures adopted should be explicitly stated to enable other workers to reproduce the results, if necessary. New methods may be described in sufficient detail and indicating their limitations. While reporting experiments on human subjects and animals, it should be clearly mentioned that procedures followed are in accordance with the ethical standards laid down by the national bodies or organizations of the particular country. Scanned certificate of ethical clearance should be provided along with manuscript manuscripts in relevant context. The drugs and chemicals used should be precisely identified, including generic name(s), dosage(s) and route(s) of administration.

The statistical analysis done and statistical significance of the findings when appropriate should be mentioned. Unless absolutely necessary for a clear understanding of the article, detailed description of statistical treatment may be avoided.

Results

Only such data as are essential for understanding the discussion and main conclusions emerging from the study should be included. The data should be arranged in unified and coherent sequence so that the report develops clearly and logically. Data presented in tables and figures should *not* be repeated in the text. Only important observations need to be emphasized or summarised. The same data should not be presented both in tabular and graphic forms. Interpretation of the data should be taken up only under the Discussion and *not* under Results.

Discussion

The discussion should deal with the interpretation of results without repeating information already presented under Results. It should relate new findings to the known ones and include logical deductions. It should also mention any weaknesses of the study.

Summary and conclusions

The summary should provide a brief account of most the relevant observations and conclusions based on the observed data only. This should be linked with the objectives of the study. Statements and conclusions not supported by the data should be avoided. Claims of ongoing studies should also be avoided.

Acknowledgment

Acknowledgment should be brief and made for specific scientific/technical assistance and financial support only and *not* for providing routine departmental facilities and encouragement or for help in the preparation of the manuscripts (including typing or secretarial assistance).

References

References should be typed on separate page after the text. The total number of References should normally be restricted to a maximum of 30. They should be numbered consecutively in the order in which they are first mentioned in the text. In the text they should be indicated above the line (superior). As far as possible avoid mentioning names of author(s) in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure or legends should be numbered in accordance with the sequence in which they appear in the manuscript.

Style of citing references

Use the style of the examples below. The titles of journals should be abbreviated according to the style used in Index Medicus. Avoid using abstracts as references. References of papers accepted but not yet published should be designated as ? in press or ? forthcoming. Authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as ? unpublished observations with written permission from the source.

Avoid citing a personal communication, unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication. Please refer http://wwwicmje.org for further details.

All references must be verified by the author(s) against the original documents.

1. Standard Journal article

List the first six authors followed by et al. The usual style is surname followed by initials as shown below

Vega KJ, Pina I, Krevsky B. Heart transplanation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980-3.

2. Organization as author

The Cardiac Society of Australia and NewZealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 124:282-4.

3.Books and other Monographs

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

4. Editor(s), compiler(s) as author

Norman IJ, Redfern SJ. editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

5. Chapter in a book

Philips SJ, Whisnant JP Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press;1995.p.465-78.

6. Unpublished Material In press

LeshnerAl. Molecular mechanisms of cocaine addiction. N Engl J Med. In Press 1996.

7. Journal article in electronic format

Morse SS. Factors in the emergence of infectious diseases.Emerge Infect Dis [serial online] 1995 Jan-Mar (cited 1996 Jun 5); 1 (1): [24 screens]. Available from: URL: http://wwwcdc.gov/ncidod/EID/eid.htm.

Tables

Type each table with double spacing *on a separate sheet of paper.* Do not submit tables as photographs. Number the tables consecutively (in Arabic numerals) in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter as footnotes, and not in the heading. For footnotes use the following symbols, in this sequence: *, t, ~, §, I I, ~[, **, tt, ~~. Explain in footnotes all abbreviations that are used in each table.

Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 x 173 mm (5 x 7 inches).

Letters, numbers, and symbols on figures should be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Photomicrographs should have internal scale markers.

Symbols, arrows, or letters used in photomicrographs should contrast with the background.

Figures should be numbered consecutively according to the order in which they have been cited in the text. Titles and explanations should be provided in the legendsnot on the illustrations themselves. **Each figure should have a label pasted on its back indicating the number of the figure and the running title.** Do not write on **the back** of figures, scratch, or mark them by using paper clips.

Legends for Illustrations (Figures)

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When **symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.**

If a **figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure.** Photographs of potentially identifiable people must be accompanied by written permission to use the photograph.

Color printing requires additional cost that will be communicated to the author.

An electronic version of the figures in JPEG or GIF should be provided for web version. The authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards.

Units of Measurements

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be given in degrees Celsius. Blood pressures should be given in millimeters of mercury. All hematologic and clinical chemistry measurements should be reported in the metric system in terms of the International System of Unts (SI). Editors may request that alternative or non-SI units be added by the authors before publication.

Abbreviations and Symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should **precede its first use in the text unless it is a standard unit of measurements.**

Proofs and reprints

Authors of accepted articles are supplied printer's proofs either by post or through e-mail. Corrections on the proof should be restricted to printer's errors only and no substantial additions/deletions should be made. **No change in the names of the authors** is permissible at the proof stage. Reprints up to 10 would be supplied as per request of the corresponding author.

UNDERTAKING BY AUTHORS

We, the undersigned, give an undertaking to the following effect with regard to our article entitled "..... ....." submitted for publication in Pulmon, the journal of Respiratory Sciences.

1. The article mentioned above has not been published or submitted to or accepted for publication in any form, in any other journal.

2. We also vouchsafe that the authorship of this article will *not* be contested by anyone whose name(s) is/are not listed by us here.

3. I/We declare that I/We contributed significantly towards the research study *i.e.,* (a) conception, design and/or analysis and interpretation of data and to (b) drafting the article or revising it critically for important intellectual content and on (c) final approval of the version to be published.

4. I/We hereby acknowledge the journal's **conflict of interest** policy requirement to scrupulously avoid direct and indirect conflicts of interest and, accordingly, hereby agree to promptly inform the editor or editor's designee of any business, commercial, or other proprietary support, relationships, or interests that I/We may have which relate directly or indirectly to the subject of the work.

5. I/We also agree to the authorship of the article in the following sequence:-

Authors' Names (in sequence)	Signature of Authors
1.	.....
2.	.....
3.	.....
4.	.....
5.	.....
6.	.....
7.	.....
8.	.....

Copyright Transfer Agreement Form

This document must be signed by all authors and submitted with the manuscript.

COPYRIGHT TRANSFER AGREEMENT

Pulmon, the Journal of Respiratory Sciences is published in 3 issues a year by the Academy of Pulmonary and CriticalC are Medicine.

The Pulmon and Authors hereby agree as follows: In consideration of Pulmon reviewing and editing the following described work for first publication on an exclusive basis:

Title of manuscript: ……..……..

The undersigned author(s) hereby assigns, conveys, and otherwise transfers all rights, title, interest, and copyright ownership of said work for publication. Work includes the material submitted for publication and any other related material submitted to Pulmon. In the event that Pulmon does not publish said work, the author(s) will be so notified and all rights assigned hereunder will revert to the author(s).

The assignment of rights to Pulmon includes but is not expressly limited to rights to edit, publish, reproduce, distribute copies, include in indexes or search databases in print, electronic, or other media, whether or not in use at the time of execution of this agreement, and claim copyright in said work throughout the world for the full duration of the copyright and any renewals or extensions thereof.

All accepted works become the property of Pulmon and may not be published elsewhere without prior written permission from Pulmon. The author(s) hereby represents and warrants that they are sole author(s) of the work, that all authors have participated in and agree with the content and conclusions of the work, that the work is original, and does not infringe upon any copyright, propriety, or personal right of any third party, and that no part of it nor any work based on substantially similar data has been submitted to another publication.

Authors' Names (in sequence)	Signature of Authors
1.	.....
2.	.....
3.	.....
4.	.....
5.	.....
6.	.....
7.	.....
8.	.....