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Academy of Pulmonary & Critical Care Medicine

Pulmon

The Journal of Respiratory Sciences

Editorial

Allergy in Air

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The term allergy was introduced by Clemens von Pirquet way back in 1906.Over the years, the concept of allergy got more clarified as type 1 hypersensitivity disorder of the immune system associated with Immunoglobulin E (IgE). Aeroallergen are the air borne substances essentially proteins or glycoproteins which are capable of binding to Immunoglobulins E (IgE) to incite an allergic reaction with an overwhelmed Th2 response in body. At birth, we have Th2 predominant immune response. With the exposure to microbes from environment, Th1 response develops and body reaches an equilibrium between Th1 and Th2 immunity eventually. Allergies have been a major concern in the western world all this while due to overt hygiene practices, preventing timely exposures and thereby persistence of Th2 allergic response. However, with the urbanization in our country wherein children are kept far off from farms and animals they also sustain a major Th2 response which makes them prone to all allergic manifestations. Atopic march has been a well known phenomenon where these individuals were found to suffer from atopic dermatitis, allergic rhinitis and atopic asthma.

There has been a strong correlation between allergic rhinitis and asthma. 20%–30% of patients with allergic rhinitis develop asthma eventually. Interestingly, 60%–80% of patients with bronchial asthma have coexisting allergic rhinitis[1]. It was Simons[2] who first proposed a common term as "allergic rhino bronchitis" as asthma and allergic rhinitis despite being heterogenous disorders with different phenotypes share a possible common link. Strengthening this fact further, Grossman[3] introduced the idea of "one airway, one disease". A common airway from nose to alveolar ducts has similar epithelium ciliated pseudostratified columnar

epithelium with goblet cells and similar physiological response when exposed to allergens.

Interaction of aeroallergens with host immunity leads to an interplay of multiple inflammatory markers[4]. In nut shell, on allergen exposure , body synthesises an antibody against it (IgE). Amount of IgE may vary as per genetic susceptibility. Mucous membrane acts as a reservoir for not only the mast cells attached with allergen specific IgE but also for basophils, CD4 T cells, macrophages, B cells and neutrophils. On subsequent exposure to allergen, bone marrow produces multiple inflammatory cells and also the progenitors which are then released in the circulation. These get locally recruited by chemo attractants to the tissue site. At local site, IgE binds to the allergen and soon forms cross linkages which leads to degranulation of mast cells to release preformed mediators especially histamines, leukotrienes, typtase and chemokines. This leads to an acute response in the airway. Even after symptoms settle, the inflammatory response continues to exude more and more cells like mast cells, dendritic cells and T cells. Th2 response takes the charge and releases interleukine-3,4,5 and 13 which further increases IgE production. This cascade reaction may give symptoms related to nasal passages like sneezing, itching and leakage or bronchial passages like wheezing, and mucus production.

Usually pollens, moulds, house dust mites (HDMs) and pets are the most common allergens[5]. The meteorological factors have a great impact on aeroallergens. Weather conditions with high temperature and humidity confine individuals to indoors. Thus, in such areas, respiratory allergies are more attributed to indoor aeroallergens, commonest being house dust mite. Air pollution and depletion of ozone layer further worsens the situation by increasing the level of proteins in outdoor ambient air. Type of aeroallergens differ not only between countries but also within the country[6]

In this issue VenuGopal and group have published a study on prevalence of type of aeroallergens in south Kerala by skin Prick Test (SPT). Some centres do the tests by using intradermal tests or scratch test. There is a need to study the sensitivity of these different methods. Expectantly they have got rice grain dust more common than other more common allergens which are almost similar to those reported in various parts of India.

Detection of respiratory allergy requires an elaborate history from patient regarding a reaction to exposure, past history of similar event, IgE levels and a positive SPT with that allergen. SPT has stood the test of time and continues to be the gold standard in establishing the sensitization to an allergen. SPT is highly sensitive and specific than other available alternatives like radio allergosorbent test (RAST) [7]. Importantly, it needs to be carefully interpreted with a history of clinical response to that allergen when exposed as a positive SPT may not always correlate with symptoms[8]. Management of nasobronchial allergies includes allergen avoidance when possible[9]. Secondly, symptomatic treatment against array of inflammatory mediators like anti histaminics, locally acting or systemic glucocorticoids and selective leukotriene receptor antagonists[10,11]. Allergen immunotherapy (AIT) has also emerged as a promising modality in a selected subset, not responding to usual therapy. However, more evidences are required before using it upfront in the therapy. As yet, pollens, dust, fungi, house dust mites and insects are the common prevalent aeroallergens in various regions of India. Only their concentration varies due to difference geo-climatic conditions. Hence there is a need of more state wise studies to know more about state wise prevalence of different aeroallergens. This would help plan a precise SPT.

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Review article

Urticaria

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Introduction

Skin is one of the largest immunological organ and is often a target for allergic and immunological response.[1] Urticarias are pruritic, oedematous, erythematous plaque lesions of variable size that blanch under pressure and often have a pale centre. Wheals are transient, and in most types of urticaria last for less than 24hours.[1,2] The lesions are round, polymorphic or serpiginous and can rapidly grow and coalesce.[3] Incidence has been reported to be around 8.8%.[4] Angioedemas are the result of a local increase in vascular permeability, often notable in the face, oropharynx, genitalia and less frequently in the gastrointestinal tract. These swellings are painful but rarely itchy. Wheals primarily affect the superficial skin layers (papillary dermis), whereas angioedema can involve the submucosa, the deeper reticular dermis and subcutaneous tissues. Wheals and angioedema can occur together or alone. Urticaria can occur alone in around 50% ,while with angioedema in 40% and angioedema alone occurs in 10% of cases.

Acute Urticaria

Acute urticaria is defined as wheals occurring for less than 6 weeks. However individual lesions usually last only 24 hrs.[2,4] Usually seen in young children and around 30% may progress to chronic urticaria[3,4]. Acute urticaria is idiopathic in about 50% of patients (acute spontaneous urticaria (ASU)), following respiratory tract infections in 40%, to drugs in 9%, and to foods in 1%.[4–6]. Up to 36% of patients with ASU can progress to CSU[6]. Foods, beta lactam antibiotics, insects, contact with an external agent, or parasites usually cause IgE dependent acute urticaria. Drugs like opioids, muscle relaxants, radio-contrast agents and vancomycin cause mast cell degranulation and proinflammatory mediator release. Complement-mediated acute urticaria can be triggered by serum sickness, transfusion reactions, and viral or bacterial infections. Acetylsalicylic acid (aspirin) and NSAIDs can cause urticaria through their effects on the metabolism of arachidonic acid[2,4,5]. Common

foods that cause urticaria are milk, eggs, peanuts, fish and shellfish. Mycoplasma pneumonia and parasitic infections have been commonly reported in children, while viral hepatitis and infectious mononucleosis are seen usually in adults[7-10].

Chronic Urticaria

Chronic urticaria is presence of daily or almost daily wheals or angioedema for more than 6 weeks with individual lesions lasting for 4-36 hours[2,6,11]. Prevalence is estimated to be 0.5-5%[3]. Women are more commonly affected with peak age of onset between 20-40 years[4,11-13].

Though cause is often elusive, chronic spontaneous urticaria (CSU) have been consistently associated with respiratory infections in 25 to 50 %. Viral infections like Hepatitis A and B, infection of nasopharynx also have been associated. CSU has been associated with Helicobacter pylori and has been shown to remit with elimination and relapse with reinfection.[6,8]

Psychosocial factors may play a role as evidenced by higher percentage of mood disorders, anxiety and personality disorders in patients with CSU. However it is still uncertain if these are a consequence of CSU.[11,19-21]

Patients with food allergy usually have intermittent symptoms and presents often within an hour of food intake.[4] Food allergy detected by skin prick testing in 25-30%, aeroallergen positivity has been reported to be as high as 60%.[10,22,23]. Common food allergens seen were hazelnut, potato, apple, oatmeal, pork, beef, and seafood.[11] Contrary to this, a study in Kerala showed that 98% of patients with chronic urticaria had some form of food allergy. Common offending food allergens were wheat (28%), garlic (22%), ground nut (20%), cashew nut (18%), prawns (17%), ginger (16%), peas (12%) and black pepper (10%)[24].

Pseudo allergens (e.g., food additives and some spices) are believed to be the cause of CU, but is controversial and few studies have shown less than 30% resolution, 10 to14 days after removal of pseudo allergens from patient's diets.[24-26] Drugs especially NSAID and ACE inhibitors are associated with CSU. NSAID can precipitate or exacerbate CSU. ACE inhibitors cause CSU by non-immunological bradykinin accumulation and often resolves with stopping the drug though symptoms can persist in some for even months beyond[28-30].

In around 45% of patients, circulating immunoglobulin G (IgG) autoantibodies that recognize IgE antibodies or the alpha subunit of the high-affinity IgE receptor on dermal mast cells and basophils are seen. They in turn lead to chronic stimulation of these cells and the release of histamine and other inflammatory mediators that cause urticaria and angioedema. CSU is also associated with antithyroid antibodies in approximately 27% of cases however antibody do not correlate with thyroid function.[12,31,32]

Table 2- **Classification of chronic urticaria**

1.Chronic Spontaneous Urticaria	
2. Chronic Inducible Urticaria	
2a. Physical Uricaria	
1.Dermographic Urticaria(urticaria factitial)	"Skin writing" Mechanical shearing forces (wheals arising after 1–5 min)
2.Delayed pressure Urticaria	Vertical pressure (wheals arising with a 3–8 h latency
3.Cold contact urticaria	Cold air/water/wind
4.Heat contact urticaria	Localized heat
5.Solar Urticaria	UV and/or visible light
6.Vibratory Urticaria	Vibratory forces, e.g. pneumatic hammer
2B. Special Types	
1.Cholinergic	Due to a brief increase of the body core temperature often secondary to exercise, passive heat or spicy food
2.Adrenergic	elicited by stress
3.Aquagenic	
4.Contact	
3.Diseases related to urticaria for historical reasons, and syndromes that present with hives and/or angioedema	
Urticaria pigmentosa	
Urticarial vasculitis	
Bradykinin-mediated angioedema (e.g., HAE)	
Cryopyrin-associated periodic syndromes (CAPS)	Familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) or neonatal-onset multisystem inflammatory disease (NOMID).
Schnitzler's syndrome	Recurrent urticarial rash and monoclonal gammopathy,recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy
Bullous pemphigoid (prebullous stage)	
Well's syndrome	Granulomatous dermatitis with eosinophilia/eosinophilic cellulitis
Gleich's syndrome	Episodic angioedema with eosinophilia
Exercise-induced anaphylaxis	

Classification of chronic urticaria
Table 2- **Classification of chronic urticaria** Modified information from [8,12]

Chronic inducible urticaria

Dermographic Urticaria/ Immediate symptomatic dermatographism

Wheals appear on stroking or scratching skin (skin writing), which causes shearing forces. Wheals appear soon within five minutes and subside in 5 to 30 minutes and are usually intensely pruritic. Young adults usually in second or third decade of life are commonly affected with mean duration of around 6.5 years. It is the most common form of physical urticaria.[33,34]

Delayed pressure urticaria/ Delayed dermatographism

Wheals which are painful appear around 4-8 hours after exposure to pressure and lesions lasts 24-48 hours. Commonly affects male in thirties. Mean duration is 6-9 years. Palms, soles and buttocks are commonly affected areas.[6,8,33]

Cold urticaria occurs on exposure to firm cold bodies, cold fluids or even cold air. Disease is more common in women and has a mean duration of 4.2 years. Disease can occur as a result of infection, neoplasia or autoimmune diseases. However it is idiopathic in most patients[8].

Heat urticaria occur on exposure to warm solids or air, while solar urticaria occur on exposure to light in the wavelengths ranging between 280 and 760 nm, with UV light being implicated in majority of cases.

Cholinergic urticaria caused by increased body temperature after physical exercise and/or emotional stress is common in young adults usually in the age group of 16-35 years. Pin sized wheals surrounded by erythema is characteristic[6–8].

Adrenergic urticaria presents with wheals with white halo often in response to stress. The disease responds to a treatment with the beta-adrenoreceptor-blocker, propranolol.[35]

Contact urticaria is defined by the appearance of wheals at sites where chemical substances have come into contact with skin. The disease can be strictly confined to the areas of contact, like in nettles (urtica urens or urtica dioica), but generalized systemic symptoms can occur, especially in IgE-mediated allergic contact urticaria. Common eliciting factors are food, plants, drugs, cosmetics, industrial chemicals, animal product and textiles.[8]

Aquagenic urticaria can be further subclassified as classical wherein water acts as carrier for epidermal antigen or salt dependent where osmotic pressure changes induce urticaria[11].

Pathophysiology[4,6,8,12]

Mast cells and basophils are the major effector cells involved in the development of urticarial lesions. Degranulation releases preformed vasoactive mediators, primarily histamine.[12,32] Mast cells can be activated by immunological (especially IgE mediated immediate hypersensitivity reaction) or non-immunological mechanisms. Histamine and other mediators, such as platelet-activating factor (PAF) and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilatation and plasma extravasation as well as cell recruitment to urticarial lesions.

IgE mediated mechanism are believed to be less important in chronic urticaria as evidenced by a lack of co-relation between disease severity and IgE levels. Though around 30-50% patients may have anti IgE or high affinity IgE receptors the significance is not known. Anti IgE is also

seen in atopic dermatitis and several autoimmune diseases.

Non-immunological degranulation is believed to induced by reactive oxygen species or compliment system (C3a, C4a, and C5a) which can act as anaphylatoxin.

Mast cell independent urticaria

Pathogenesis is believed to be due to prostaglandin release from the epidermis rather than histamine from mast cells. Common examples include development of contact urticaria to sorbic acid, cinnamic acid, cinnamic aldehyde, methyl nicotinate or dimethyl sulfoxide. These patients do not respond to antihistamines, but rather to acetylsalicylic acid and NSAIDs.[6,8,12]

Diagnosis

Diagnosis is primarily based on history and clinical examination while investigations may be usually supportive or confirmatory in some cases. A detailed history regarding onset, duration, associated symptoms, location, severity, potential triggers, recent infection, drug intake, illicit drug use, occupation, stress, response to prior therapy, family history of atopy, sexual history etc[3,8,11,12,31].

Causes of Urticaria	
Immunoglobulin E (IgE) mediated	**Nonimmunologically mediated**
Aeroallergens	Contact allergen
Contact allergen	Elevation of core body temperature
Food allergens	Food pseudo allergens
Insect venom	Light
Medications	Mastocytosis
Parasitic infections	Medications (direct mast cell degranulation)
Non-IgE immunologically mediated	Physical stimuli
Aeroallergens (proteases)	
Autoimmune disease	
Bacterial infections	
Cryoglobulinemia	
Fungal infections	
Lymphoma	
Vasculitis	
Viral infections	

Table 3[3,8,12,36]

Urticaria-Associated History and Physical Examination Findings with Possible Etiologies

Clinical clue	*Possible etiology*
Abdominal pain, dizziness, hypotension, large erythematous patches, shortness of breath, strider, tachycardia	Anaphylaxis
Dermatographism, physical stimuli	Physical urticaria
Food ingestion temporally related to symptoms	Food allergy
High-risk sexual behaviour or illicit drug use history	Hepatitis B or C (cryoglobulinemia) virus, human immunodeficiency virus
Infectious exposure, symptoms of upper respiratory tract or urinary tract infections	Infection
Joint pain, uveitis, fever, systemic symptoms	Autoimmune disease
Medication use or change	Medication allergy or direct mast cell degranulation
Pregnancy	Pruritic urticarial papules and plaques of pregnancy
Premenstrual flare-up	Autoimmune progesterone dermatitis
Smaller wheals (1 to 3 mm); burning or itching; brought on by heat, exercise, or stress	Cholinergic urticaria
Thyromegaly, weight gain, cold intolerance	Hypothyroidism
Travel	Parasitic or other infection
Weight loss (unintentional), fevers, night sweats	Lymphoma
Wheals lasting longer than 24 hours,	Urticarial vasculitis (Figures 7 and 8)

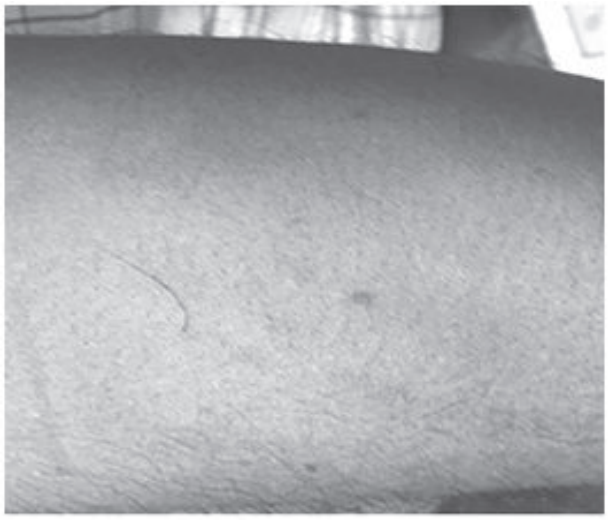
Table 4

With chronic urticaria or in acute cases a nonspecific workup including a complete blood count with differential, erythrocyte sedimentation rate and/or C-reactive protein testing, liver enzymes, and thyroid-stimulating hormone measurement may be done to rule out underlying causes. When history is suggestive of a physical urticaria, challenge testing with standardized physical stimuli can confirm the diagnosis. Allergy testing is not recommended unless there is specific indication of an allergic cause.[3,4,12]

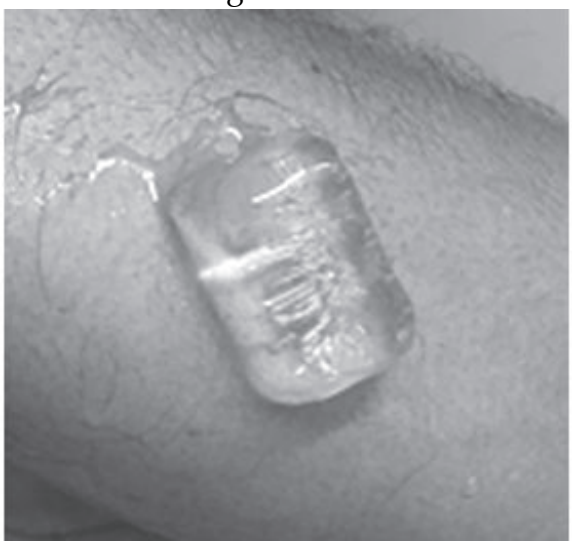
Routine skin biopsy is not recommended but may be done to rule out vasculitis or in resistant cases. Biopsy may show a neutrophilic infiltrate or an eosinophilic infiltrate or a mixed pattern. Neutrophilic infiltrates often co-relate with poor response to antihistaminic.[37,38]

Cold urticaria can be diagnosed by provocation test which include an ice cube challenge test in which an ice cube, melting in a see-through plastic bag, is placed on the skin for 5 min. 10 min after removal of the cube a local wheal will develop. (Fig 1) A shorter or longer provocation time may be used e.g., 30 s (in patients who are very sensitive or afraid of strong reactions) and up to 20 min (in patients with a positive history but no reaction after 5 min).[38–40]

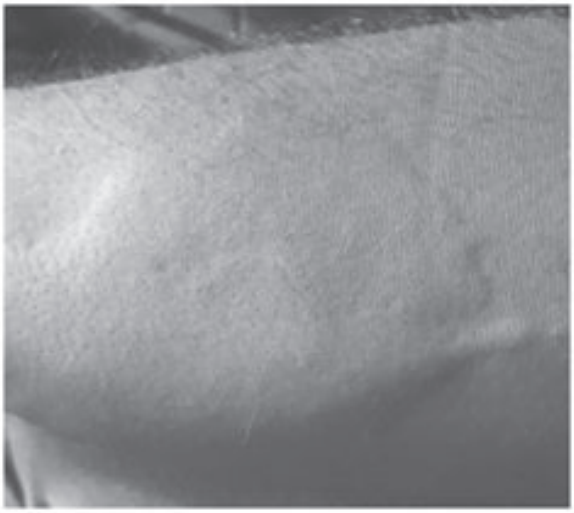
Other methods include testing with cool packs or cold-water baths (e.g., an arm can be submerged in cold water at 5-10°C for 10 min) and Temp*Test*® measurements. Because of the risk of causing systemic reactions, cool packs, and cold-water baths should be used with caution. Temp*Test*® is a Peltier effect-based cold provocation device that allows exposure of the skin to thermal elements with defined



a. Before testing



b. Provocation with ice cube



c. Development of cold urticaria

Fig 1: Cold provocation test

temperature and hence may be used in cold as well as heat urticaria. Heat urticaria can also be diagnosed by skin testing with metal or glass cylinders filled with warm water or a warm water bath for 5 minutes. Urticaria appears after 10 minutes. Usually temperatures between 45°C and 36°C are tested.[39–41]

Urticaria factitia can be diagnosed by using dermographometer which can be used to apply shearing force from 20-60 gm/mm^2 .[39,41]

Solar urticaria can be diagnosed by applying UV-A (6 J/cm2), UV B (60 mJ/cm2) and visible light from 10 cms for 10 minutes which results in wheal and flare reaction.[42,43]Delayed pressure urticaria can be diagnosed by applying different weights to the skin, which exert a defined pressure on the skin surface. Dermographometer can be used, applying vertically to the back skin a pressure of 100 g/ mm^2 for 70 s. Results recorded after 6 hrs is considered as positive, if a delayed red palpable swelling occurs.[39,41]

Contact urticaria can be diagnosed by patch test (open application or with occlusion) which is applied for 20 min on healthy and on previously damaged skin. The area should be examined after 30 min and after 24 hrs if protein contact dermatitis is suspected. A normal skin prick or patch test can be performed. Alternatively, the patient can be exposed in a controlled way. Finally, specific IgE measurements may be helpful.[44,45]

TYPE	SUBTYPE	ROUTINE TEST	DIFFERENTIAL DIAGNOSIS TESTS
Spontaneous urticaria	Acute urticaria	None	None
	CSU	CBC, ESR, TSH	Test for infections, thyroid function test thyroid antibodies, functional autoantibodies, skin biopsy
inducible urticaria	Cold urticaria	CBC,ESR, cold provocation test	Test for cryoproteins
	Pressure urticaria	CBC, ESR, pressure test (dermographometer, fric test)	None
	Heat urticaria	CBC,ESR, heat provocation test	None
	Solar urticaria	CBC, ESR, UV and visible light threshold test	Rule out other light induced dermatoses
	Symptomatic dermographism	CBC, ESR Dermographometer-threshold testing	None
	Vibratory angioedema	Test with vortex	None
	Aquagenic urticaria	Wet clothes at body temperature for 20 minutes.	None
	Cholinergic urticaria	Exercise and hot bath provocation	None
	Contact urticaria	Cutaneous provocation tests	None
ESR Erythrocyte sedimentation rate: CBC Complete blood count: TSH Thyroid stimulating hormone: CSU Chronic spontaneous urticaria: UV Ultraviolet			

Table 5

Treatment

The therapeutic approach to CU involves

a. The identification and elimination of underlying causes

b. The avoidance of eliciting factors

c. Tolerance induction

d. Pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators

In most cases of physical urticaria agents can be avoided or exposure minimised by measures like using sunscreens in solar urticaria or lamps with UV filter.

Plasmapheresis may be tried in severe cases with functional autoantibodies.

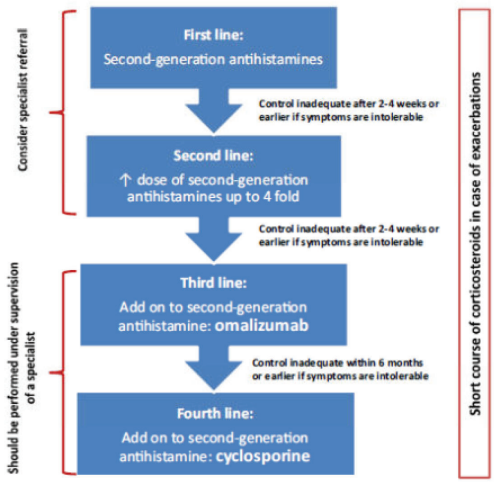
A pseudo allergen-free diet, containing only low levels of natural as well as artificial food pseudo allergens, has been tried in and may be useful at least partially in many patients.

Inducing tolerance can be useful in some subtypes of urticaria. Examples are cold urticaria, cholinergic urticaria and solar urticaria, where a rush therapy with UV-A has been proven to be effective within 3 days.[12]

Symptomatic pharmacological treatment

Pharmacological management of urticaria involves antihistamines, leukotriene antagonists, omalizumab,corticosteroids, immuno suppressants like cyclosporine, etc. If 4 times the regular dose of anti histaminics proves ineffective, leukotriene receptor antagonist may be added, but evidence do not suggest significant benefit. Following which a course of omalizumab can be given and if there is no response after 6 months, a trial of cyclosporine (3-5mg/kg/day) can be given. In severe cases oral prednisolone in doses of 20-50 mg can be used over short periods of time (14 days). Alternative options that have been found to be useful in severe refractory cases are sulfasalazine, dapsone, hydroxychloroquine, colchicine, mycophenolate mofetil, 5-aminosalicylic acid, intravenous immuno globulin G (IVIG), rituximab, warfarin etc. Danazol has been used in cholinergic urticaria.[3,4,6,8,]

Usual agents ands doses of anti histaminics commonly used are given in table 6



Cetirizine	10-20 mg
Desloratadine	5 mg
Fexofenadine	120 mg
Loratadine	10 mg
Bilastine	20 mg
Rupatadine	10 mg

Table 6

Cold urticaria can be treated with cold desensitisation but requires gradual exposure of increasing skin surface area to cold water above threshold temperature but have to be done daily to maintain a desensitised state.[46–48] Other treatment option includes second generation antihistaminics which can be dosed up to 4 times the usual dosage.[12,49,50] Patients who achieve remission can have doses reduced to minimum level that prevents symptoms. Patients who do not respond to usual therapy can be treated with omalizumab which can bring symptomatic relief with doses of around 300 mg every 4 weeks for a period of 12 months. When symptom remission occur antihistaminics can be tapered.[51–53] Other option includes cyclosporine.[54] Etanercept and benralizumab may be used in some selected cases.[55,56] Glucocorticoids may be used but are usually ineffective in most patients.[54] Montelukast may be useful in some patients.[57]

Solar urticaria can be treated with antihistaminics. Glucocorticosteroids either topical or oral can be used when antihistaminics alone are ineffective. Other treatment options include omalizumab, psoralen plus ultraviolet A (PUVA) radiation and narrowband UVB, plasmapheresis, cyclosporine. Plasmapheresis may be used alone or in conjunction with PUVA therapy. Intravenous immunoglobulin at doses ranging from 1.4 to 2.5 g per kg may be given over two to five days. Desensitisation may be tried but effects usually last only a few days.[58,59] Vibratory angioedema can be treated well with exposure prevention. Antihistamines are usually effective. Disease refractory to multiple antihistamines, antileukotriene agents, dapsone,cyclosporine, prednisone, and omalizumab may respond to ketotifen, a strong antihistamine and mast cell stabilizer, given at a dose of 1 to 2 mg twice daily.[60,61]

Aquagenic urticaria can be treated with antihistaminics. Omalizumab can be used. Some patients respond to propranolol at doses of 10 to 40 mg daily. Stanozolol was found effective in a patient with HIV infection, hepatitis C virus infection, and aquagenic urticaria, who had failed therapy with oral antihistamines. Barrier creams may be useful in some.[62,63]

Heat urticaria can be treated with combination of H1 and H2 antihistamines. Desensitisation with daily hot bath may be useful.[64,65]

Cholinergic urticarias can be treated with antihistaminics. However in case second generation fails, hydroxyzine a first-generation agent can be attempted. Ketotifen, omalizumab and anabolic steroid danazol have been reported to be effective.[66]

Delayed pressure urticaria often does not respond to antihistamines alone. Other agents that are effective include omalizumab, montelukast, dapsone, sulfasalazine, non-steroidal anti-inflammatory drugs. Oral steroids are the most effective treatment, but doses above 30 mg per day may be necessary, hence unsuitable for long-term use.[67]

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Original Article

Prevalence of aeroallergens in nasobronchial allergy: A descriptive study from South Kerala

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Abstract

Background: Nasobronchial allergy in the form of allergic rhinitis and asthma is commonly encountered. Aeroallergens are usually responsible for this clinical condition. Identifying the offending allergens and avoidance is one of the most important measures which may help in the management of nasobronchial allergy. Skin prick test is one of the most reliable and safe method of identifying aero allergens.

Methods: This descriptive study was conducted to identify the skin sensitivity to various aero allergens in patients with nasobronchial allergy and to study the regional pattern of aero allergens in south Kerala. 104 atopic patients with complaints of nasobronchial allergy were selected for the study. Skin prick allergy testing with 36 aero allergens were performed in the above patients by skin prick test method.

Results: All the patients (100%) with nasobronchial allergy had sensitization to at least one aeroallergen. Common offending allergens were rice grain dust (56.7%), house fly (55.7%), house dust mite (51.9%), cockroach (49%), paper dust (48%), cotton dust (38.4%), wheat grain dust (37.9%), ant (37.5%) and hay dust (36.5%) .

Conclusions: Sensitization to aero allergens is common in asthma and allergic rhinitis. Skin prick test is a reliable and safe method to identify aero allergens. Most common offending aero allergens were rice grain dust, house fly, house dust mite, cockroach, paper dust, cotton dust, wheat grain dust, ants and hay dust.

Key words: Aero allergens, Nasobronchial allergy, Allergy testing, Ig E, Skin prick testing (SPT). MeSH terms: Aero allergens, Nasobronchial allergy, Skin prick testing (SPT). Pulmonary Medicine, Government TD Medical College, Alappuzha

Introduction:

Aeroallergens are airborne substances which triggers an allergic reaction. They play an important role in the pathogenesis of allergic diseases, particularly asthma and rhinitis. Pollen, house dust mites, fungi, animal danders, domestic pets, and insects are of major importance as triggering factors.

Allergic diseases such as asthma, allergic rhinitis and atopic dermatitis are increasing in epidemic proportions all over the world including developing countries like India. The possible role of aeroallergens and other sensitizing agents in its etiopathology is increasingly evident with the advancement in the molecular, and immuno biological understanding of the such diseases. Structure and function of allergens are now well elucidated which in turn throw light on the relationship between allergic sensitization, allergen exposure, and clinical manifestations.

Detection of aeroallergens sensitization is of paramount importance in diagnosis and optimizing the management of patients with nasobronchial allergy[1,2]. However, the extent and degree of aeroallergen sensitization in different regions is diverse and multiple factors influence it. Airborne pollen and their concentration vary in different periods depending upon the blooming seasons, environmental conditions and change in economy and lifestyle[3, 4] .

Studies conducted in western countries shows that skin test reactivity to perennial aeroallergens is more correlated with asthma[5] and to pollen is closely associated with allergic rhinitis[6].Several aerobiological studies have been conducted in various parts of India to determine the pneumatic concentration and seasonality of pollen grains and fungi. A recent study from VP chest institute Delhi revealed that pollens, dusts, fungi, and insects were important sensitizing aeroallergens in patients with allergy in northern region of India[7].

Skin allergy testing through skin prick test (SPT) is a simple and reliable method to demonstrate hypersensitivity to a specific antigen. The test is found to be more sensitive and specific than radio allergo sorbent test (RAST)[8] for establishing allergic sensitization. The present study was carried out to investigate the pattern of skin prick test reactivity to various aeroallergens among patients with nasobronchial allergy ie rhinitis and/or asthma.

Objectives:

1) To study the prevalence of sensitization to aero allergens among patients with nasobronchial allergy.
2) To study skin sensitivity to various aero allergens in patients with nasobronchial allergy.
3) To identify the regional pattern of sensitization to aeroallergens in Alappuzha district of Kerala

MATERIALS AND METHODS

This descriptive study was conducted at Alappuzha, a district of Kerala, India. Data was collected from patients with nasobronchial allegry during their visit to the outpatient unit of department of Pulmonary Medicine, Government TD Medical College Hospital Alappuzha.

Inclusion criteria

Atopic patients with complaints of allergic rhinitis, asthma or both who consented were selected for the study.

Exclusion criteria

Non atopic patients with normal or mildly elevated serum Ig E levels (less than 250 IU/ mL), patients below the age of 10 and above the age of 60 years, patients having rhinitis due to non allergic cause (Vasomotor rhinitis, purulent rhinitis, etc) and people showing gross dermatographism were excluded from the study. Those with acute or uncontrolled urticaria were also not included, because of the difficulty in doing skin testing in such patients. Since the study was aimed to identify the regional pattern of aero allergy, patients outside Kerala were also excluded from the study.

Methodology

A detailed history of past incidences of nasobronchial allergy was taken in all patients. The patient's atopic status was evaluated by probing into a history of any other allergies in the past like asthma, allergic rhinitis, skin allergy or food allergy. Total serum IgE was estimated in all patients by fully automated Bi-directional Interfaced Chemo luminescent immunoassay method to assess the atopic status.

Allergy testing with 36 aero allergens was performed in the above patients by skin prick test method. List of the allergens tested are given in table 1. Skin testing and reading were conducted as per criteria by American Academy of Allergy Asthma and Immunology[9] (AAAAI) and British Society for Allergy and Clinical Immunology[10] (BSACI) guidelines for the management of drug allergy. Patients were asked not to take antihistamines or steroids 72 hours prior to testing. The reaction was checked at 15-20 minutes. Buffered saline was used as negative control and histamine as positive control. A positive reacton is a weal size of diameter of 3mm or more greater than negative control, surrounded by a flare.

Results:

Total number of patients: 104

Sex distribution: Male -58 (55.7%), Female -46 (44.2%)

Age: ranged from 11 to 59 with a mean of 35.4 years

44 patients were suffering from allergic rhinitis, 20 from asthma and 40 had both allergic rhinitis and asthma together.

Serum IgE levels: The serum IgE values ranged from 250 IU/mL to 8774 IU/mL, with an mean value of 1268 IU/mL.

Pattern of sensitization:

All the patients (100%) with nasobronchial allergy had sensitization to at least one aeroallergen. All the patients except one with nasobronchial allergy are sensitized to multiple allergens. The number of allergens to which the patients were sensitized varied from 2 to 13 with an average of 6 antigens.

Most common offending aero allergens were rice grain dust (56.7%), house fly (55.7%), house dust mite (51.9%), cockroach (49%), paper dust (48%), cotton dust (38.4%), wheat grain dust (37.9%), ant (37.5%) and hay dust (36.5%) . The allergens to which patients were least allergic include pollens of cocos nucifera, eucalyptus, heteropogan, a grass (only 1 patient each) and aspergillus fungus (only 2 patients).

None of the 104 patients developed any immediate or late complications following skin prick testing (SPT).

No relation could be established between age, sex , symptomatic status, and IgE level of the patient and the number or type of aero allergens.

nasobronchial allergy were rice grain dust, house fly, house dust mite, cockroach, paper dust, cotton dust, wheat grain dust, ants and hay dust respectively in the order of frequency. It was observed that indoor aeroallergens were equally important and insects like house fly,

Sl No	Allergen	No. of patients found to be allergic No (%)	Sl No	Allergen	Number of patients found to be allergic No = %
1	Hay Dust	24	18	Imperata	2
2	Paper Dust	22	19	Cenchrus	12
3	Cotton Dust	22	20	Argemone	8
4	Rice Grain Dust	54	21	Oridoxa	2
5	Wheat Grain Dust	38	22	House dust mite	51
6	Heteropogan	2	23	Spider web dust	12
7	Ageratum	12	24	Housefly	58
8	Parthenium	10	25	Cockroach	50
9	Cocos nucifera	1	26	Mosquito	40
10	Carica papaya	4	27	Ant (Red)	39
11	Eucalyptus sp.	1	28	Aspergillus niger	2
12	Ricinus communis	12	29	Aspergillus flavus	1
13	Amaranthus	14	30	Penicillium sp.	2
14	Areca cachu	10	31	Aspergillus fumigates	2
15	Dodonea viscose	4	32	Cow dander	24
16	Acacia arabica	6	33	Cat dander	1
17	Mangifera indica	2	34	Chicken feather	12

Table 1: List of aero allergens tested and frequency of sensitization

Discussion

The results of our study showed that the sensitizing aeroallergens among patients with

mosquito , cockroach, ants and others like house dust mite were major aeroallergens responsible for sensitization. This is more or less comparable with the findings of studies on

aroallergerns in asthma and rhinitis conducted in Delhi by Kumar R et al except for paper dust for which sensitization was much lower in their study[7].

The allergens to which patients were least sensitized include pollens of cocos nucifera, eucalyptus, heteropogan, and aspergillus fungus. Sensitization to cocos nucifera aero allergen is not studied elsewhere and its low level of sensitisation despite its wider use in this part of the world is interesting as earlier studies from our centre have shown that coir, a product from the husk of cocos nucifera is an important agent in the induction/ causation of nasobronchial allergy[11].Similarly low sensitisation was also seen with cat dander though cat as domestic pet is very common in this area .Many studies have shown that cat antigens are important sensitizing agents for asthma and asthma like symptoms[12]. These findings in our study may warrant further research.The variation in the prevalence of aeroallergen sensitization in different regions could be due to the diverse geoclimatic condition and /or adaptation of specific microbiological flora and fauna in specific meteorological conditions pertaining to each place.

Strengths and limitations of the study

The patients participated in this study were representative of the population in the Alappuzha district of Kerala, though the data is hospital based and the number of patients were less in number. This is the first and only study from Kerala which looked in to the pattern and prevalence of aeroallergens in nasobronchial allergy.

Our study could help to understand the prevalence of regional aeroallergen sensitization and appropriate measures can be taken to avoid potential allergens. Avoidance of houseflies, and house dust mite , cockroaches and paper dust may result in improvement of symptoms in allergic patients and may result in non appearance , delay in onset or milder symptoms in those who are allergy prone [13]. Meteorological changes greatly influence the concentration of airborne pollen and we strongly recommend the use of regional pollen calendars which can provide important pollen season for grass, weeds and trees for the use of clinicians as well as patients to establish chronological association between the concentration of pollen in air and seasonal allergic symptoms.

This study will help to select the panel of most common aeroallergens for skin prick testing and will also help in choosing the most implicated allergens for immunotherapy in this area.

Aero allergens show considerable cross reactivity between various agents and significantly contribute to sensitization and causation of symptoms. However we did not address this issue as it is too complicated and challenging[14].Our study was a hospital based one and a large community based study among patients with nasobronchial allergy is needed.

Conclusion:

We conclude that sensitization to aeroallergens is quite common among patients with nasobronchial allergy and skin prick testing is an efficient and safe method to identify aero

allergens. Our study showed that most patients with nasobronchial allergy are sensitized to multiple allergens and commonly encountered allergens, in the order of prevalence are rice grain dust, house fly, house dust mite, cockroach, paper dust, cotton dust, wheat grain dust, ants and hay dust. The study did not show any relation between age, sex, symptoms, serum IgE levels of the patient and the number or variety of sensitive allergens.

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Radiology Pearl

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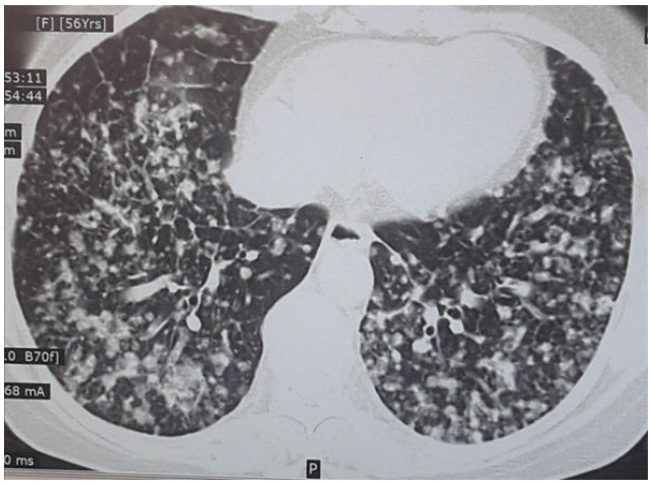
A fifty year old lady came with complaints of cough for about 6 months duration. Clinical examination showed crepitations over the base of both lungs.
Her HRCT thorax is given below.
What is the radiological sign called?

Fig 1



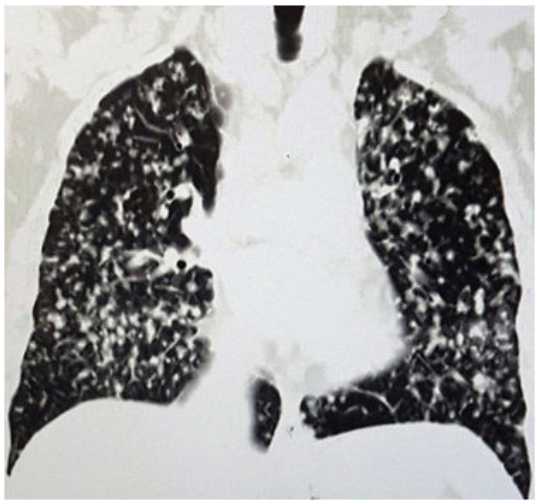
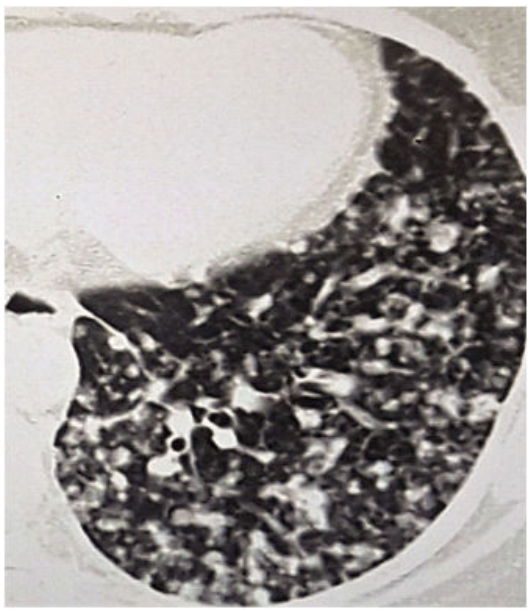


Fig 2



Answer:

The 'Cheerio sign'

'Cheerio sign' refers to pulmonary nodules with a central lucent cavity as seen on CT. It is due to proliferation of (malignant or non-malignant) cells around an airway. They are so named because of their resemblance to the breakfast cereal, Cheerios (Fig 4). This is a rare finding which is mostly associated with malignancies but can also been seen in non malignant conditions.

The common association is with Adenocarcinoma lung. It can be seen in pulmonary metastases, Pulmonary Langerhans cell histiocytosis, and pulmonary meningothelial- like nodules (rare). The lesion may be mimicked by rheumatoid nodules, Granulomatous polyangiitis, lymphoma etc also.

In this case, biopsy from larger lesions done by Interventional radiologist revealed adenocarcinoma lung with metastases. She underwent chemotherapy from Tata Cancer hospital, Mumbai and her review x-ray showed fair resolution of the shadows.

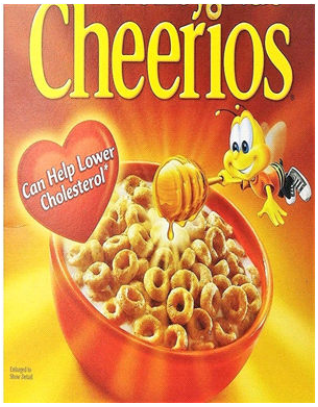


Fig. 4

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Spirometry Pearl

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The Case

A 64 year old gentleman, reformed smoker, presented with cough and chest tightness for 2 months. He had no medical comorbidities. After physical evaluation, he was subjected to a postero-anterior chest radiograph and spirometry. The flow time curve and flow volume loop with relevant values are depicted in fig 1.

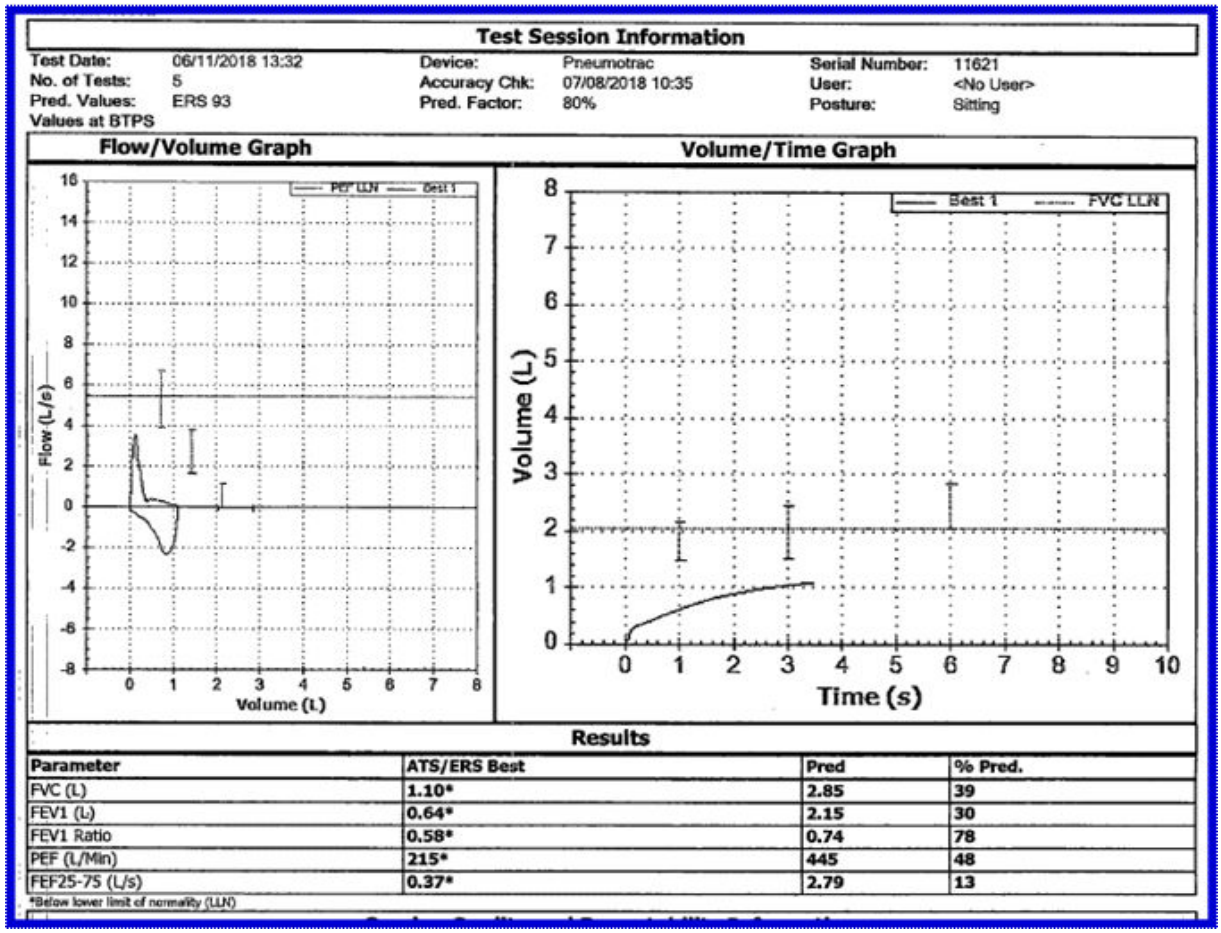

Fig 1 – Spirogram of the patient

What is this pattern termed and what does it signify?

Answer

Biphasic flow volume curve (sequential filling – emptying pattern)

Usually signifies obstruction to one main bronchus by a structural lesion.

Discussion

Spirometry is an invaluable tool in the diagnostic armamentarium of the pulmonologist. The test is helpful in the evaluation of undiagnosed respiratory symptoms, quantifying severity of functional lung impairment, sequential follow up of respiratory disease states and monitoring response to therapy. In addition to the information provided by studying various lung volumes, specific patterns of the flow volume loop are diagnostically useful. One such pattern is the biphasic curve or bi-compartmental flow volume loop, which is characteristic of the obstruction of a main bronchus.

Reports linking unilateral obstruction of a main bronchus producing characteristic patterns in the flow volume curve have been available for decades. Gascoigne et al in 1990 gave the first description of biphasic curve when studying the flow volume loop in two patients with obstruction of main bronchus[1]. The mechanism for the characteristic pattern of flow volume loop was also provided by the authors, which was in lines with the earlier descriptions of Roos and Braat.[2] The ***"two compartments sequential filling – emptying theory"*** whereby unilateral obstruction to airflow in a mainstem bronchus manifests as a delay (slow flow rate) in the end inspiratory and end expiratory limb of the flow/volume curve, was postulated to explain this observation.

The appearance in the flow volume loop is striking and characteristic. The inspiratory limb of the flow-volume loop shows an end inspiratory "tail" (of low constant flow rate) and the forced expiratory limb had a biphasic shape with normal initial curvature but a "straight line" (slow constant flow rate) appearance in later expiration. During forced expiration the initial half or so of the vital capacity is expired normally and rapidly, giving a normal initial curvature to the expiratory spirogram. The second half of the vital capacity is expired much more slowly, giving the spirogram a straight line appearance. Similarly, the inspiration limb also exhibits a pronounced slowing of maximum inspiratory flow towards the end of inspiration. The graph is a reflection of the fact that emptying and filling of either lung occurs as a distinct compartment, one fast and the other much slower. The slower compartment corresponding to the lung whose main bronchus is severely narrowed, and the faster (normal) compartment is the unaffected lung. The unaffected lung dominates the early part of forced expiration or inspiration, so that the contribution of the slowly ventilated lung becomes evident only in the second half of the manoeuvre.

The biphasic pattern of the spirogram is diametrically the opposite of that seen with tracheal stenosis.[3] In this scenario, a fixed obstruction in the trachea with fixed airflow resistance throughout the respiratory cycle results in virtually constant flow in the first part of expiration and hence the characteristic "straight spirogram"; in later expiration flow declines, causing curvature ofthe spirogram,

because at smaller lung volumes maximum expiratory flow is no longer determined by the tracheal narrowing but results from dynamic compression of intrathoracic airways.

The biphasic pattern, although characteristic, is uncommon and can be produced by lesions of multiple etiologies, most of which share a common functional domain of critical obstruction of a main bronchus.[4] The differential described include malignant neoplasms, mediastinal cysts, Wegener's granulomatosis[5], relapsing polychondritis[6], unilateral pulmonary emphysema or MacLeod's syndrome, main stem bronchial obstruction after single lung transplantation etc. The aforementioned mechanism of asynchronous emptying of the two lungs would also be expected with diffuse airway disease affecting only one lung, as in hypoplastic conditions (such as Macleod's syndrome) or in the resident lung after unilateral transplantation for emphysema even in the absence of main bronchial involvement.

Coming back to our patient, though not mentioned in the initial description to facilitate discussion, physical examination revealed features of right lung collapse (tracheal deviation to right side, lower mediastinal shift to right, elevated right diaphragm and absent breath sounds over right chest). Chest radiograph (fig 2) confirmed the right lung collapse and CT chest showed the location of tumor to be at 1.5 cm from carina. Bronchoscopy and biopsy revealed squamous cell carcinoma and ultrasound abdomen showed metastatic liver lesions. He was initiated on palliative chemotherapy.

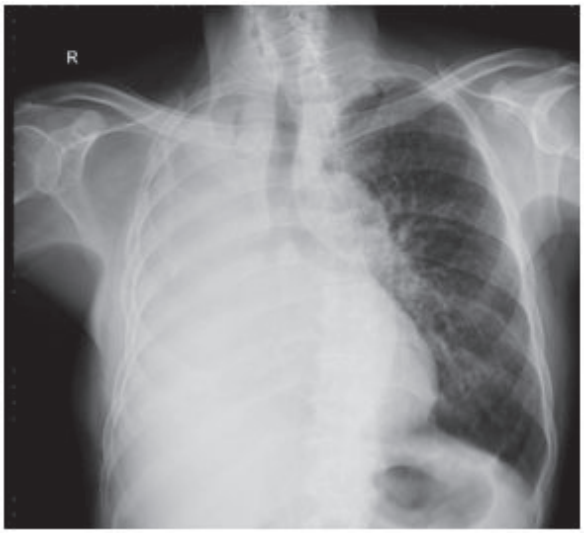

Fig 2 – Posteroanterior chest radiograph of the patient at presentation

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Articles Invited

The Pulmon, official publication of Academy of Pulmonary and Critical Care Medicine (APCCM) invites articles in the form of original research papers, review articles,case reports, radiology pearls,and letters to the editor.The articles which are original and plagiarism free should be prepared in MS Word with double column in single spaced typed pages . The same should be submitted to the editor electronically as an attachment on E mail ID *editorpulmon2019@gmail.com*. All articles will be subjected to plagiarism check and standard review process.

Certificate of appreciation and cash awards will be given for best articles in each category (original research paper, case report and radiolology pearl) every year at the annual national conference of the academy.

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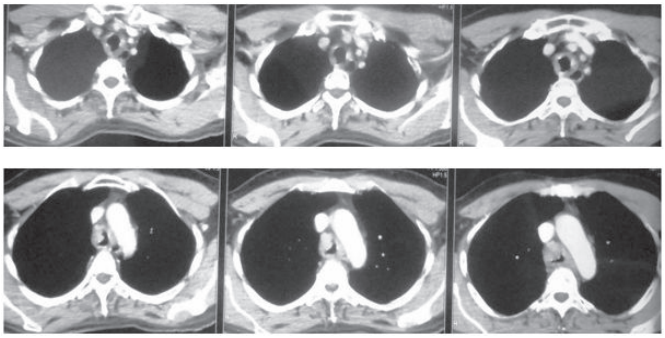
- Dr.R.C.Babu Memorial award for the best original paper published in Pulmon- Certificate plus Rs 5000/-
- Best case report-Certificate plus Rs 2000/-
- Best radiology pearl- Certificate plus Rs 2000/-

Editor in Chief Pulmon

Self assessment quiz

Vishnu Sharma.M
Professor and head, Respiratory medicine,
A J Institute of Medical Sciences, Mangalore

Figure 1



Question 1: What is the most likely diagnosis?

1. Tracheal stenosis
2. Malignant tracheal tumor
3. Esophageal carcinoma
4. Benign tracheal tumor
5. Bronchogenic carcinoma

Question 2: Which of the following is the MOST COMMON tracheal malignancy?

1. Squamous cell carcinoma
2. Adenoid cystic carcinoma
3. Carcinoid
4. Adenocarcinoma
5. Lymphoma

Question 3: Which of the following is the MOST COMMON secondary tracheal tumour?

1. Bronchogenic carcinoma
2. Esophageal cancer
3. Thyroid cancer
4. Head and neck cancer
5. Invasion by adjacent lymph nodes

Question 4: Which is a WRONG statement regarding tracheal tumors?

1. Smoking is a known risk factor for squamous cell carcinoma of trachea.
2. Diagnosis of tracheal tumors is usually delayed due to non specific symptoms.
3. Symptoms of tracheal tumor often mimic that of obstructive airway diseases
4. Surgery is the treatment of choice
5. Squamous cell carcinoma of trachea can present with hemoptysis.

Question 5: What is the treatment for this patient with tracheal tumor who presented with stridor?

1. Tracheostomy
2. Laser resection
3. Radiotherapy
4. Chemotherapy
5. Brachytherapy

Answers

Question1: Malignant tracheal tumor.
CT scan shows intra luminal lesion with irregular inner surface extending to a large length in the trachea which is highly suggestive of malignant lesion[1]. Tracheal tumor which involves a large length of trachea is usually

Adenoid cystic carcinoma. In this case it was confirmed by biopsy.

Question 2: Most common primary malignant tumor of trachea is squamous cell carcinoma[2]. As such primary tracheal tumors are uncommon.

Question 3: Most common secondary tracheal tumour is invasion by adjacent lymph nodes[3]. Secondary tracheal tumors are more common than primary tracheal tumors. Most of the secondary tracheal tumors are due to direct extension from adjacent structures and invasion by secondary lymph node in neck.

Question 4: Wrong statement is 4. Only localised malignant tracheal lesion can be operated[4]. When the lesion is diffuse or involves larger length of trachea palliative treatment with endoscopic de bulking/ stent placement/ radiotherapy/ chemotherapy may have to be done.

Question 5: In this patient the tumor is involving a large length of trachea. Hence it is not operable. Palliation can be achieved by laser resection[4].

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Case report

A common clinical symptom with an uncommon etiology

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Abstract

Pleurisy is a commonly encountered scenario in pulmonary practice which manifests as pleuritic chest pain. Pleural inflammation, pleural effusion and peripheral parenchymal lesions of the lung abutting the pleura can result in pleuritic pain. The differential diagnosis of pleuritic pain ranges from infections, inflammatory states (like connective tissues diseases), pleural involvement due to primary or metastatic malignancies, pulmonary embolism, trauma, drug induced or radiation induced pleural injury etc. A focused history, targeted physical evaluation and limited battery of tests (chest radiograph, computerised tomography of chest and pleural fluid evaluation) will unmask the etiology in the vast majority of cases. We describe the case of a young gentleman who presented with pleuritic chest pain, where the initial workup was not rewarding. On evaluation with a CT scan of the chest, he had pericardial fat necrosis as the cause of his symptoms. He responded to conservative measures.

Key words

Pleurisy, pleuritic pain causes, pericardial fat necrosis

Introduction

Pleural diseases are commonly encountered in day to day pulmonary practice. Pleural disorders represent one of the most common reasons for consultation of a pulmonologist , and an estimated 1.5 million new pleural effusions are identified every year in the US alone; these effusions are caused by more than 60 distinct disease processes[1]. Approximately 150,000 of these effusions are caused by malignancy, lung and breast cancer being the most common culprits due to parietal pleural involvement in advanced disease[2]. Other common causes of pleural effusions

include congestive heart failure, pleural space infections, pulmonary embolism, and manifestations of connective tissue diseases such as lupus or rheumatoid arthritis. Diseases of pleura typically present with pleuritic chest pain. In addition, large pleural effusions cause chest tightness, shortness of breath and varying levels of respiratory compromise based on the amount of accumulated fluid and the baseline cardiopulmonary status of the individual. Careful clinical evaluation coupled with pleural fluid tests will clinch the etiology in most subjects.

Pleuritic pain due to pleural inflammation can occur in the absence of clinically appreciable amount of pleural fluid, which makes the differential diagnosis even more challenging. Viruses are a common causative agents of pleuritic chest pain. Coxsackie viruses, respiratory syncytial virus, influenza, parainfluenza, mumps, adenovirus, cytomegalovirus, and Epstein-Barr virus are commonly described pathogens[3]. The symptoms are self-limiting in these situations and require careful exclusion of other causes of pleurisy having more concerning consequences.

Pericardial disease can cause pleuritic pain due to spilling of the inflammation to overlying pleura. We describe the case of a young gentleman who had pericardial fat necrosis as a cause of his pleuritic pain.

Case history

A 37 years old gentleman, staff nurse by profession, working in the middle east, with no addictions presented with history of left sided pleuritic chest pain of 7 days duration. He was assessed by a physician in middle-east, and a provisional diagnosis of musculoskeletal pain was made; he was advised analgesics. There was inadequate symptom relief which prompted him to come to his home town for revaluation. On interrogation, he had no fever, cough or wheezing. There was no history of atopy. He had grade 2 dyspnoea during same period. Physical examination of cardiovascular and respiratory systems was unrewarding. Initial blood reports revealed normal total and differential blood count. Renal and liver functions as well as glycaemic status were normal. Serum C-Reactive protein levels were below 5. Considering the left sided chest pain ECG and troponin I levels were also done both of which came as normal. A chest radiograph – posteroanterior projection (Fig 1) showed left lower zone haziness.

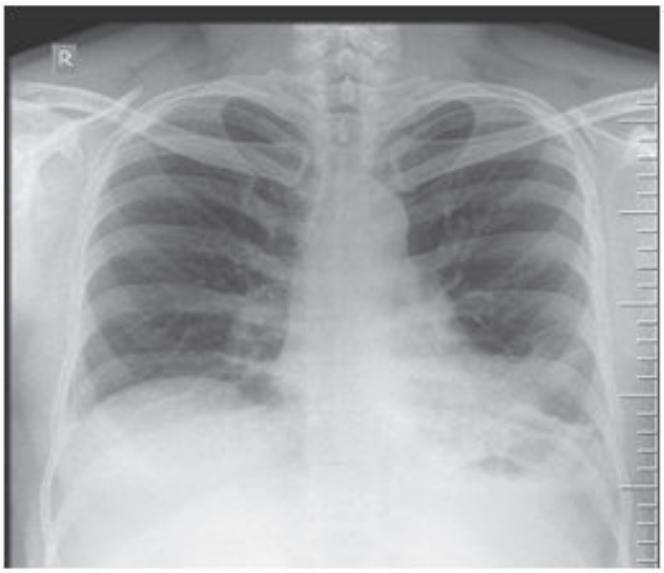

Fig 1 - Chest x ray PA view showing left lower zone paracardiac haziness

A two-dimensional ECHO and cardiac enzymes were normal. Tread mill test was borderline positive for inducible ischemia and hence a coronary angiogram was done. The angiogram turned out to be normal. His connective tissue markers also were negative. He was managed with symptomatic and supportive medications. He improved symptomatically in the next 2 weeks. Follow up chest radiograph and CT chest done at 1 month showed good resolution. He continues to be in clinical follow up.

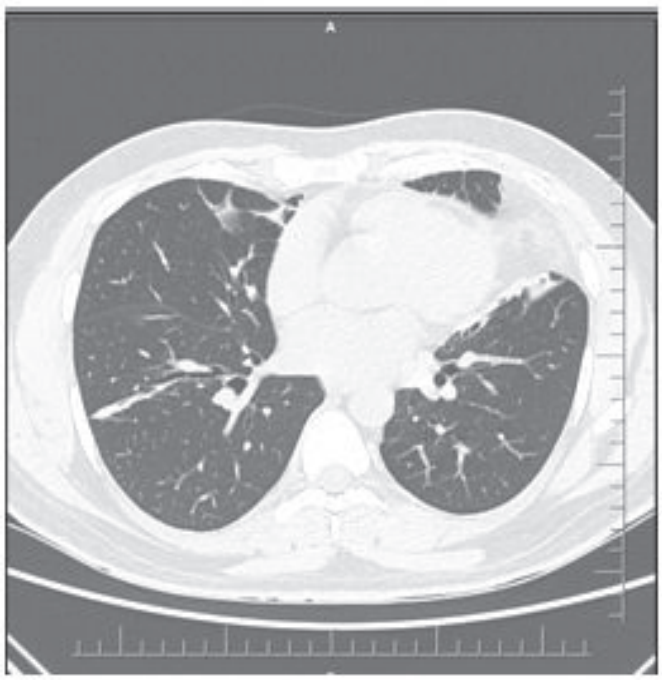

Fig 2 A – CT chest – lung window showing hyper-attenuating pericardial fat

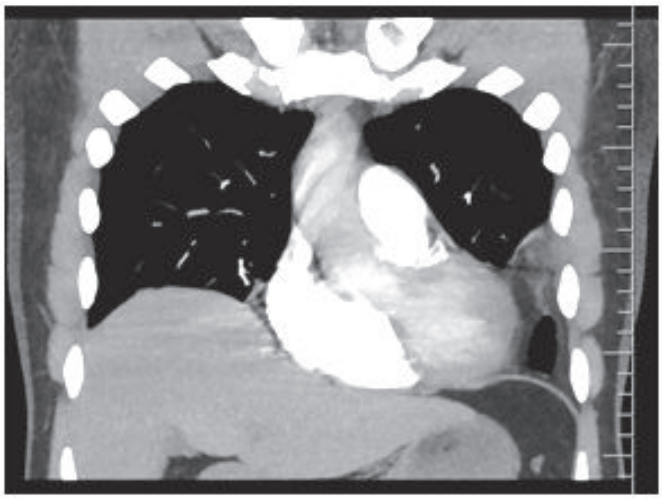

Fig 2 B – CT chest – mediastinal window – coronal image showing prominent pericardial fat with fat stranding and minimal fluid within it.

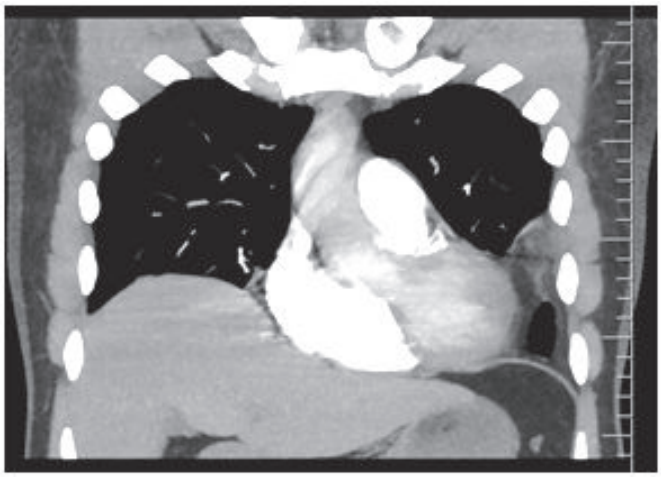

Fig 2 C - CT chest – mediastinal window showing pericardial fat stranding extending up to the costal pleura

Discussion

Pleuritic chest pain is a cardinal symptom of pleural disease although diseases involving peripheral lung parenchyma also produce the same features. The pain is described of as having a sharp catching nature which often limits the patient from taking deep breaths. There are many differential diagnoses for pleuritic chest pain of which most are indolent, but a few can be life threatening. The visceral pleura is devoid of any pain receptors and pleuritic chest pain originates from parietal pleura. The peripheral part of parietal pleurae and lateral hemidiaphragm are innervated by intercostal nerves. Irritation of these regions results in pain along the distribution of these nerves and it can be felt along the lateral part of chest.

Any disease which causes an inflammation near pleura will result in pleurisy. Apart from lung, diseases involving some adjacent structures can also cause passive

pleural inflammation. The pleural pain may be of cardiovascular origin in case of myocardial infarction, pericarditis, myocarditis, aortic dissection or aortitis. Abdominal diseases like liver / splenic abscess and pancreatitis can present with pleuritic chest pain. Uraemia causes pleuritis due to the effect of toxic metabolites. Vascular pathologies like Vasculitis, fat necrosis and pulmonary embolism with infarct can also present with pleuritic chest pain. Rarely osteomyelitis of ribs and mediastinitis also can have pleural pain as a presenting symptom[4].

Apart from thorough history and physical examination, chest x-ray and ECG are the most helpful tools to sort out between differentials. In our case the ECG was normal. Chest x ray showed left lower zone haziness. Since features of pneumonia were conspicuous by their absence, non-infectious causes were entertained and worked up proceeded accordingly. CT chest gave the conclusive evidence for pericardial fat necrosis and ruled out alternate pathology like pneumonia, thromboembolism and pleural effusion.

Pericardial fat necrosis is a benign, rare and self-limiting condition. It was first reported in 1957. It can mimic acute myocardial infarction, acute pericarditis and pulmonary embolism by virtue of similarity in symptoms. The pericardial or visceral layer of fat tissue is found in the inter-ventricular groove and it extends to the right and left pleural surface. It is more prominent in obese individuals. This fat pad undergoes necrosis and give rise to symptoms. The exact aetiology of pericardial fat necrosis is not clear although various postulates have been put forward. Torsion of vascular pedicle, rapid rise in intra thoracic pressure (as happens with weight lifting, Valsalva manoeuvre etc), pre-existing structural lesions (like lipoma, hamartoma and lipomatosis) etc have been implicated in the etiopathogenesis[5]. There is no age or gender predilection. Most common presentation is pleuritic chest pain, but dizziness, syncope, dyspnoea, palpitation and profuse sweating have also been described. The symptoms may be mistaken for a myocardial infarction. Physical examination is usually unremarkable. ECG and cardiac enzymes remain unaffected.

Pericardial fat necrosis should be suspected when patients present with acute chest pain but have no systemic symptoms and when chest radiograph, laboratory tests and echocardiography reveal no abnormalities. CT chest is the investigation of choice for the diagnosis of pericardial fat necrosis and the findings are characteristic. Chest radiography can be normal, but left paracardiac haziness, with or without concomitant pleural effusion may be seen. The typical CT finding is a lesion of fat attenuation surrounded by the increased attenuation of the anterior mediastinal paracardiac fat adjacent to the pericardium[6,7]. In obese individuals, it is not uncommon to see some amount of normal paracardiac fat, especially in patients with exogenous obesity, such as steroid therapy. Other causes of mediastinal fat stranding are mediastinitis and mediastinal abscess, but these conditions have additional CT findings and dramatic clinical consequences. Treatment is essentially

symptomatic and supportive. Symptoms usually settles in a week but can persist as long as four months. Rarely surgical excision of necrotic fat mass may be done[8].

Summary

The case narrates a 37-year-old gentleman who presented with pleuritic chest pain. The chest radiograph showed left lower zone haziness and the differentials include infectious pneumonia, pulmonary infarction, encysted pleural effusion etc. A contrast enhanced CT of the chest secured the diagnosis as pericardial fat necrosis and conservative treatment was instituted. This case is being reported because of the rarity of the condition as well as it being a radiological and clinical mimicker of some graver and potentially life-threatening diseases. The value of CT chest in the differential diagnosis of intrathoracic lesions cannot be overemphasised. Pericardial fat necrosis may be kept in mind as a distinctly uncommon differential diagnosis of pleuritic pain.

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Case report

An unusual case of ILD

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ABSTRACT: Antisynthetase syndrome (AS) is an uncommon connective tissue disease characterized by the presence of antibodies to aminoacyl tRNA synthetase along with features of interstitial lung disease (ILD), myositis and arthritis. We present a case of 30 yr old female who presented withchronic cough and exertional dyspnoea and was diagnosed with AS based on clinical findings, radiological features and serology.

Introduction

Idiopathic inflammatory myopathies are a heterogenous group of acquired muscular diseases characterized by various types and degrees of skeletal muscle inflammation[1]. Antisynthetase Syndrome (AS), firstly described by Marguerie et al. in 1990, forms a major subgroup of these inflammatory myopathies. It is characterised by the production of antibodies to aminoacyl tRNA synthetase, with anti-Jo-1 being the best known of these antibodies associated with myositis, interstitial lung disease, Raynaud's phenomenon, arthritis, fever, and "mechanic's hands"[2,3]. Prevalence of AS in the general population is unknown. Cohort studies have indicated that 20-25% of patients diagnosed with Polymyositis (PM) or Dermatomyositis (DM) have AS[4]. Women are affected 2–3 timesmore than men. The age at onset among adults ranges from 19 to 82 years with a mean age at onset varying from 43 to 60 years. Very few children and adolescents with AS have been reported[5].

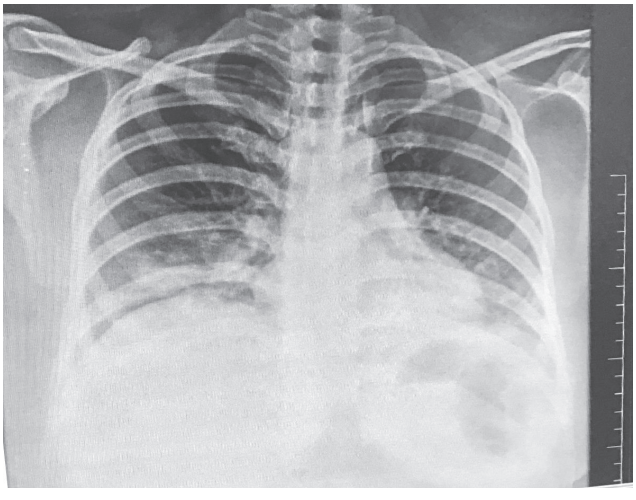


Fig1.CXR showing B/L Lower zones non homogenous opacity

Case report

A 30 yr old female with no comorbidities presented to the outpatient department with complaints of chronic cough since 5 months, non radiating central chest pain and exertional dyspnoea (mMRC gr 1-2). She also complained of multiple joints pain including major joints like knee, wrist and elbow. There was no history of morning stiffness, rashes over the body or exposure to pets and had no chronic use of medications. Patient denies having shortness of breath or wheeze in the past. She was treated with multiple course of antibiotics, inhaler medications and a short course oral steroid, but without significant relief. On examination she was mildly tachypnoeic with RR=22/min. No pallor, icterus or clubbing was present. She was mildly hypoxemic withSPO2=86-88% on room air. Routine blood investigations showed normal WBC counts with ESR =100. IgE levels were normal. Liver and renal function test were normal. Urine routine was also normal. Chest X-ray showed non-homogenous opacity over B/L Lower zones (fig1).

High resolution computed tomography(HRCT) of chest showed ground glass opacities(GGO's) in bilateral upper lobes and middle lobe, alveolar opacities with air bronchogram in bilateral lower lobe areas(fig 2,3).

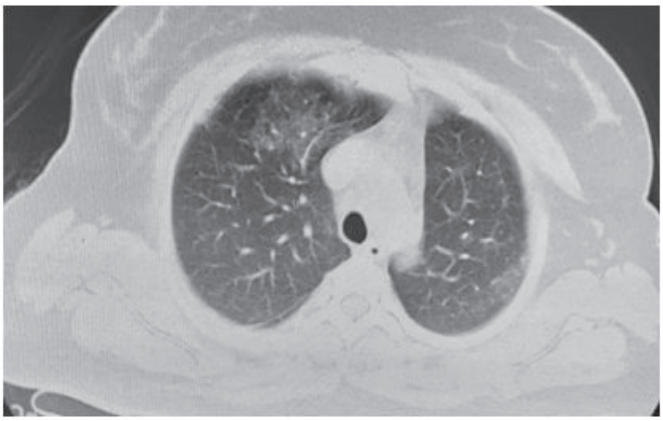


Fig.2:CT chest showing GGO's involving B/L upper Lobes

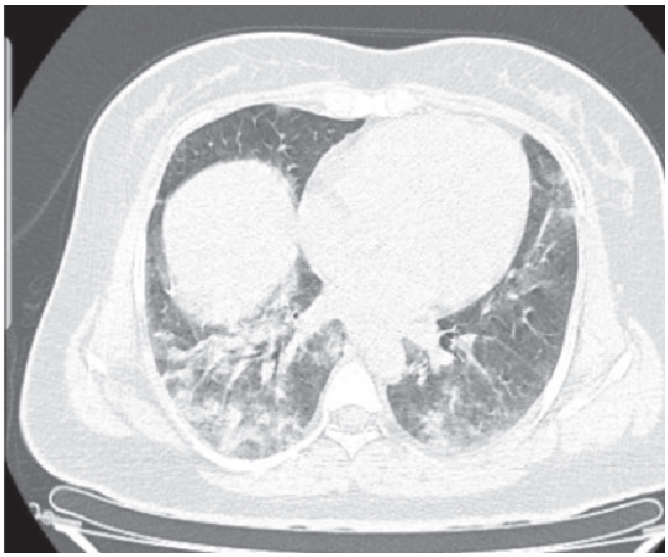
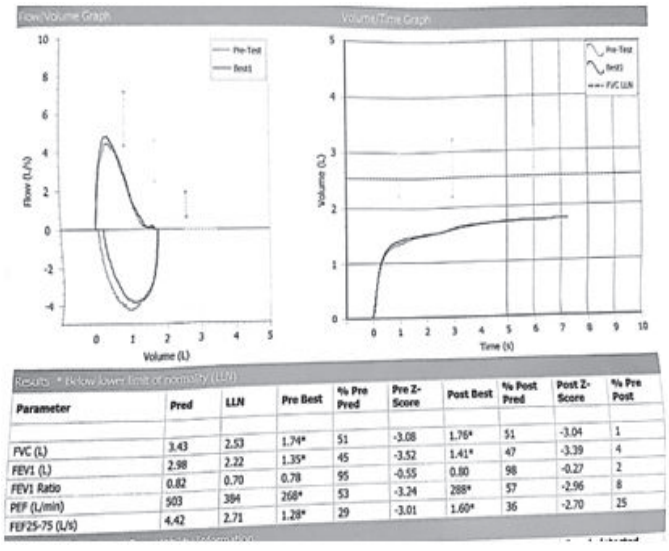


Fig3.CT chest showing alveolar opacities with airbronchogram involving B/L Lower lobes

Cardiac evaluation was normal. RA factor was positive (34 IU/ml), anti CCP was negative. Since the patient was not producing any sputum, bronchoscopy was done. Bronchoalveolar lavage (BAL) examined for AFB smear, Xpert MTB, bacterial and fungal infections were negative. BAL cytology was negative for malignant cells. Pulmonary function test (PFT) showed mixed pattern with FEV1/FVC=0.78, FEV1=47%, FVC=51 %(fig.4).



Parameter	Pred	LLN	Pre Best	% Pre Pred	Pre Z-Score	Post Best	% Post Pred	Post Z-Score	% Pre Post
FVC (L)	3.43	2.53	1.74*	51	-3.08	1.76*	51	-3.04	1
FEV1 (L)	2.98	2.22	1.35*	45	-3.52	1.41*	47	-3.39	4
FEV1 Ratio	0.82	0.70	0.78	95	-0.55	0.80	98	-0.27	2
PEF (L/min)	503	394	268*	53	-3.24	288*	57	-2.96	8
FEF25-75 (L/s)	4.42	2.71	1.28*	29	-3.01	1.60*	36	-2.70	25

Fig.4: PFT showing mixed pattern

Antinuclear antibodies (ANA) immunofluorescence was positive and showed cytoplasmic pattern. Antinuclear cytoplasmic antibodies (ANCA), antiproteinase-3 (anti-pr3) antibodies, antimyeloperoxidase (anti- mpo) antibodies, anti-double stranded DNA (anti dsDNA) antibodies were all negative. Patient was discharged on oral steroids (40 mg/ day) and home Oxygen. She was reviewed after 1 week. ANA profile showed presence of anti-jo-1 and anti ro antibodies. Creatine kinase levels were normal. By the time patient's finger tip had become thickened and hyperkeratotic – the so called "mechanic's hand" (Fig.5).

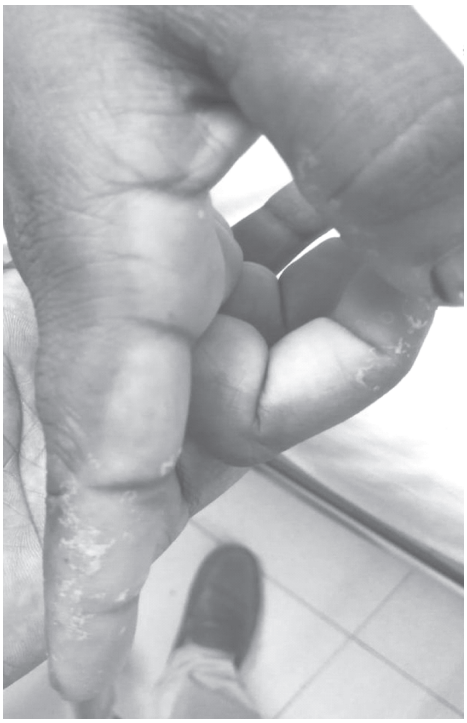


Fig.5: Thickened, hyperkeratotic, skin along the radial margins of the fingers ("mechanic's hands").

A diagnosis of Antisynthetase syndrome was made based on clinical, radiological features and serology. She was treated by rheumatologist with pulse dose (1gm for 3 days) of methyl prednisolone and cyclophosphamide (15mg/kg/month). Following a week's treatment patient had symptomatic relief and was discharged on oral prednisolone (1mg/kg body wt.) and cyclophosphamide.

Discussion

Antisynthetase syndrome was first described by Marguerite and co-workers in 1990. It is an uncommon multisystem connective tissue disease (CTD) characterized by the presence of circulating antiaminoacyl tRNA synthetase (ARS) antibodies and clinical features of interstitial lung disease (ILD), inflammatory myositis and polyarthritis. Other clinical features include fever, mechanic's hand and Raynaud's phenomenon (RP) [6]. The three major clinical criteria for the diagnosis of AS include ILD, myositis and arthritis; whereas the minor criteria includes the presence of mechanic's hands, RP and fever. Presence of anti-aminoacyl-tRNA synthetase antibody plus two major criteria or one major and two minor criteria are required to make a diagnosis of AS. Although inflammatory arthritis is included as a major criterion, some still consider it as a minor criterion[7].

Cough and dyspnoea are the major respiratory symptoms seen in 40-60% of patients at presentation[8]. The respiratory symptoms are mainly due to the presence of ILD . The onset of ILD precedes the onset of myositis in 33%, while myositis and ILD can develop simultaneously in 60%[3]. Clinically on auscultation patient may have bibasilar end inspiratory fine crepitations. Clubbing may be absent. PFT and HRCT should be considered

in all patients suspected of AS. PFT shows a restrictive abnormality with a reduced DLCO. On HRCT, three common patterns are seen in patients with AS: a non specific (NSIP) pattern, Organizing pneumonia (OP) pattern, or mixed NSIP-OP pattern. Rarely, AS presents with usual interstitial pattern (UIP). Commonly, the ground-glass opacities and consolidation are basal predominant and peribronchovascular in distribution[9]. Pulmonary hypertension may develop with or without concomitant ILD. Other pulmonary manifestations include pleuropericardial effusion and venous thromboembolism.

Fever may be present at the onset of disease or may be associated with relapse. Raynaud phenomenon develops in about 40% of patients. Some have nailfold capillary abnormalities[10]. Arthralgias and arthritis are often seen (50%), with the most common form being a symmetric polyarthritis of the small joints of the hands and feet. It is typically nonerosive but can sometimes be erosive and destructive. The following joints are commonly affected: distal and proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbow, and knees. Rheumatoid factor is found in increased frequency, especially in patients with articular involvement. In patients presenting with atypical features of RA (negative cyclic citrullinated peptide antibody status, and nonerosive arthritis), AS should be considered as a differential diagnosis due to its potential overlap.

Muscle involvement is seen in more than 90% of patients, but is usually subclinical, manifested by transient creatine kinase elevation only, which may normalize after therapy is initiated. Weakness of the pharyngeal muscles may cause dysphagia and makes these patients susceptible to aspiration pneumonia. Involvement of the diaphragmatic and intercostal muscle may lead to shortness of breath. Myocarditis has also been reported. In about 30% of patients, the skin of the tips and margins of the fingers becomes thickened, hyperkeratotic, and fissured, the appearance of which is classically described as mechanic's hands.

Demonstration of antiARS antibodies in the serum remains the main criterion for diagnosis of AS. Till date, nine different antiARS antibodies have been described, the commonest being antiJo1 antibody directed against histidyl tRNA synthetase. Others include antiPL7 (threonyl tRNA synthetase), antiPL12 (alanyl tRNA synthetase), antiOJ (isoleucyl tRNA synthetase), antiEJ (glycyl tRNA synthetase), antiKS (asparaginyl tRNA synthetase), antiYRS or anti Ha (tyrosyl tRNA synthetase), antiZo (phenylalanyl tRNA synthetase) and antiWa (directed against NEFA, a tRNArelated protein) antibodies[11]. Anti -Jo-1 antibody was named after John P, a patient with polymyositis and interstitial lung disease, in whom it was first detected in 1980[12]. Presence of anti-Jo-1 antibody is associated with acute symptoms, and the myositis is usually steroid responsive. Often, anti-Ro52, SS-A antibodies are present concurrently in patients with antiJo-1 syndrome[13]. ANA may be negative or if present shows cytoplasmic pattern. AntiARS antibodies cause cytoplasmic staining instead of nuclear staining on indirect immunofluorescence[14]. When evaluating a

patient with ILD and features suggestive of CTD, ANA is usually done as a screening test and if found negative other other antibodies are not looked for. As a result, the diagnosis of AS is missed, and such patients are often labelled as IIP or UCTD (Undifferentiated connective tissue disease). In contrast to the earlier belief that AS is protective against cancer, several recently published case studies have reported various malignancies occurring within 6 to 12 months of the diagnosis of Antisynthetase syndrome. The debate as to whether these are chance associations or causal (a paraneoplastic phenomenon) has not been resolved at this time[15].

Glucocorticoids are considered the mainstay of treatment. Patients should be advised that long-term use of glucocorticoids is necessary, though the response is variable. Standard practice is to initiate treatment with high doses for the first 4 to 6 weeks to achieve disease control, followed by a slow taper over the next 9 to 12 months to the lowest effective dose to maintain remission. Patient with severe disease form shall require pulse doses (1000mg for 3-5 days) of steroids. Patients not tolerating steroids or poor response to steroids shall require additional immunosuppressants. The commonly used drugs are Cyclophosphamide, Methotrexate and Azathioprine. Cyclosporine has also been successfully used in a case of interstitial lung disease associated with anti Jo-1 syndrome[16]. Rituximab, a monoclonal antibody to B-lymphocyte antigen CD20, can also be used successfully in refractory disease, including refractory interstitial lung disease[17].If skeletal muscles are only involved; patient shows good response to steroids. However, involvement of lung carries a poor prognosis.

Our patient was diagnosed based on clinical, radiological and serological marker showing presence of Anti-jo-1 antibody. Reported cases of AS are in the age group from fourth to seventh generation. Even in the case series from India, reported by Mathura VN et.al[18], the average age group of patients with AS were 43. 8yrs.Our case seems to be the first reported youngest case from India, at the age of 30.

Conclusion

AS is an under recognised, yet treatable cause of ILD with true prevalence unknown. We would like to emphasize the need to consider the possibility of AS in young patients presenting with ILD alongside having features of arthritis and myositis.

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