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Editor-in-chief PULMON
Dr. Venugopal. P
Professor & Head
Dept. Pulmonary Medicine
Govt. T.D. Medical College,
Alappuzha, Kerala, India - 688005
E mail: editorpulmon2019@gmail.com

Advertising and tariff requests
Dr. Vipin Varkey,
Treasurer APCCM
33/4567, m6/29
Mukkuzhickal
KSHB Housing Colony
Malaparamba
Kozhikode - 673009
Ph: 04952378060, 9446262485
E mail : treasurerapccm@gmail.com

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Editor
Dr.Venugopal P.
Professor & Head
Dept. of Pulmonary Medicine
Govt. T.D. Medical College
Alappuzha, Kerala, India - 688005
Email: editorpulmon2019@gmail.com

Academy of Pulmonary & Critical Care Medicine

Pulmon

The Journal of Respiratory Sciences

Editorial

The second wave of covid-19 – what changed in India?

C.M.Anusha[1], Kesavan Nair[2]

[1]Corresponding author:Senior Resident , Department of Pulmonary Medicine, Shree Uthradom Thirunal Academy of Medical Sciences, Thiruvananthapuram
Email ID: cmanusha@gmail.com
[2]Professor ,Department of Pulmonary Medicine, Shree Uthradom Thirunal Academy of Medical Sciences, Thiruvananthapuram

The outbreak of coronavirus disease 2019 (COVID-19), which began in Wuhan, China, in late 2019, has spread to 203 countries as of March 30, 2020, and has been officially declared a global pandemic.[1]

Nearly after 6 months of the peak of September 2020, Covid-19 cases in India once again started rising in 1st week of March making way for the so-called second wave.[2] Like the the Spanish flu in 1918-20, the second surge of Covid-19 has been more devastating than the first one[3]. Data says that this wave is proving to be deadlier and more infectious, although death rate is still low.[4] The second wave refers to those who will suffer in the medium-term due to measures taken to limit the spread of COVID-19. It includes, among many others, those who delay presenting to healthcare facilities for fear of COVID-19 infection; those with progressive diseases whose appointments are rescheduled; and those who miss routine screening. Third wave is the effect of virus on social determinants of health and its effects on next generation.[5] The question of how doctors, particularly those working in primary care, will navigate the backlog remains unanswered.

Younger affected more?

When the analysis was done by ICMR DG, there was no major shift in the age group in both waves. More than 70% of the patients in both waves were more than 40 years of age, only a marginal higher proportion of younger patients.[2]

Older population still seem to have higher death rates

Data released by the Centre shows that in seven age groups up to 70 years, the prevalence of deaths in this wave is comparable to the prevalence in the last wave. However, in the age groups 70-80 and above 80, mortality rates are higher in the second wave are higher (Image 2). It is still the older population who is at higher risk and needs to be protected. However, the number of deaths is high in all age groups because there are more cases. And with the virus becoming more infectious and some mutations escaping the immune response, the younger population needs to strictly follow Covid-19 appropriate behaviours.[3]

Sharper rise in cases

There has been exponential rise in number of covid-19 cases. On 18 June last year, India recorded 11,000 cases and in the next 60 days, it added 35,000 new cases on average every day.

On 10 February, at the start of the second wave, India confirmed 11,000 cases - and in the next 50 days, the daily average was around 22,000 cases. But in the following 10 days, cases rose sharply with the daily average reaching 89,800.[4] This may be owed to super spreading events like marriages, social gatherings. Another explanation could be due to ADE (Antibody dependent enhancement – It's a phenomenon in which sub optimal antibodies will enhance the entry of virus into its host cell through phagocytic or complement pathway, followed by replication

Symptom Analysis

According to ICMR, this wave mainly had asymptomatic cases, might have been one of the causes for rampant number of cases due to inadequate quarantine and contact tracing.

Table 1:Data Courtesy- TOI Apr 19, 2021

Infected	First wave	Second wave
<30 years	31%	32%
30-40 years	21%	21%

Table 2: Data courtesy- Indian express, May 5, 2021

Age group	1st wave	2nd wave
<10	0.27%	0.34%
10-20	0.53%	0.31%
20-30	2.08%	1.72%
30-40	5.27%	5.39%
40-50	11.98%	10.82%
50-60	23.29%	21.23%
60-70	28.76%	28.21%
70-80	19.99%	22.17%
80+	7.82%	9.81%

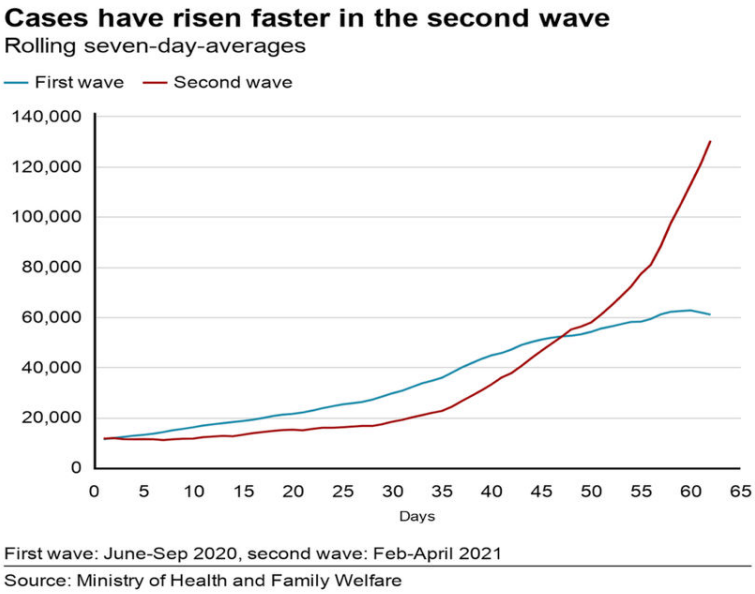

Fig. 1

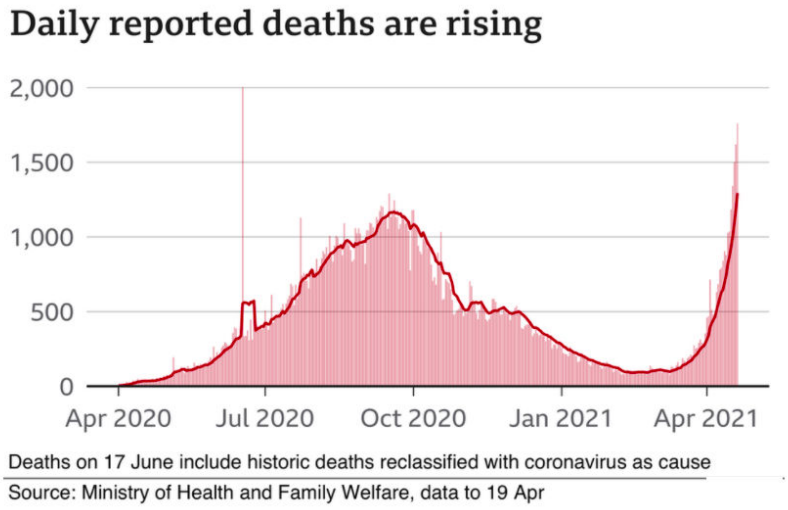

Fig. 2

Higher proportion of symptomatic cases got admitted in second wave. Higher proportion of admitted patients showed breathlessness in second wave. Patients with sore throat and dry cough were higher in first wave.

Also, it was observed that the hospital admissions were seen on day 7 onwards of illness owing the fact that people preferred to undergo home isolation and treatment. The hypoxemia was seen set in 2nd week onwards once the cytokine storm flared up. The other hospital admissions were accountable to due to the aftermath of covid-19 infections like Long Covid syndrome, Pulmonary embolism, Mucormycosis , Candidiasis etc. as compared to the previous wave where hospital admission were mainly due to Acute Covid-19 illness .

Death rates same?

However, death rates have seem to be appeared the same in both second and first waves in hospitalized patients

Third wave possible?

That is going to be decided by mass vaccination drive by the government and Covid-19 appropriate behavior by everyone. As per Sutra Model(a mathematic project to predict covid-19 trajectory) , there is a possibility of a third wave , affecting the pediatric populations , if vaccinations aren't ramped up.[6] Also, further mutation of virus seems to be a major deciding factor too. We need to strengthen the safety protocols and rapidly vaccinate people and also need to keep an eye on the mutations. If all of this is achieved, the numbers could be reduced significantly.

So, lessons learnt so far….

While this ferocious second wave has India very hard, we must learn few important lessons here.

1.Vaccination is the key to bring down the pandemic by achieving her immunity and protecting another outbreak

2.The second wave stresses upon the urgent need to focus on pandemic preparedness planning. State governments and central agencies need to invest in stockpiling minimal inventory of essential medicines and medical supplies at critical centres to provide industry-adequate buffer time to cater to demand surges. Surveillance systems need to be installed to identify and track outbreaks and contain spread within hotspots. Quarantine protocols need to be calibrated to the transmission and spread of the virus

3. We need to ramp up genomic sequencing of covid-19 virus to identify the new strains as early as possible so that strategies can be reworked based on mutant strains.

4. There is need to have better data on seropositivity rates of the country. For example , if the population who are already infected with covid-19 are identified, the need not be vaccinated. It would be better to deploy these vaccines in low seropositivity rates[7,8,9,10]

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MID PULMOCON 2022

Alappuzha Respiratory Society (ARS) &
Academy of Pulmonary and Critical Care Medicine (APCCM)

Dear Colleagues,

It gives us great pleasure to welcome you all to Alappuzha, the land of serene beatches, lush green paddy fields, cocunut lagoons and breathtaking backwaters for the mid-term annual National Conference of Academy of Pulmonary & Critical Care Medicine (APCCM) jointly organized by Alappuzha Respiratory Society (ARS) and APCCM.

We are planning to conduct the conference on May 15, 2022 Sunday as a one day event. The scientific committee is working relentlessly and we assure you the content of this scientific programme will offer the latest and most significant developments in various areas of Pulmonary Medicine. The exact venue of the conference will be intimated shortly.

Looking forword for the pleasure of hosting you all at Alappuzha
With very warm personal regards,

Dr. P.S. Shajahan
President, APCCM

Dr. B. Jayaprakash
Secretary, APCCM

Dr. P. Venugopal
Organising Chairman

Dr. K. Venugopal& Dr. Arjun Suresh
Organising Secretaries

Incorporating palliative care principles to improve symptom control and quality of life in patients with chronic pulmonary diseases

Shoba Nair

Introduction

'A 75 year old retired school teacher has a diagnosis of chronic obstructive pulmonary disease (COPD) since many years. Of late, he has been using home-based long-term oxygen therapy (LTOT) and BiPap during night hours. He is again seeking admission to the hospital and it is his fourth admission this year. He is cachectic with a pigeon chest and struggling to breath, in spite of NIV support and oxygen'.

Clinical scenarios like the above are familiar to pulmonologists. The gentleman has advanced progressive illness with poor prognosis and poor quality of life. What are the different aspects of his suffering? Physically, he is short of breath and emotionally he might be very anxious. Functionally, he might be feeling helpless and unable to do self-care, let alone doing things that he enjoyed before. Spiritually, he might be having no sense of purpose or meaning in life and might even be waiting for the ordeal to end. Clinicians looking after such patients might be wishing them away. Can incorporating the principles of palliative care help such patients to live comfortably and to die with dignity?

Pulmonary disease trajectories

Morbidity and mortality are extremely high in advanced lung diseases causing un-necessary suffering[1] Lung cancer, COPD, Interstitial lung disease (ILD), Pulmonary hypertension, and Cystic Fibrosis are chronic lung diseases that patients suffer from. Lung transplant forms another group of patients with high mortality and morbidity. Lung cancer patients have a period of gradual progression and disease control with oncology interventions[2] They often experience a tipping point where they become increasingly symptomatic followed by a short period of evident decline. Disease trajectories in COPD and lung fibrosis are characterized by uncertainties and they are variable. They do experience gradual decline punctuated with acute exacerbations[3] . Every exacerbation can be life threatening and hospital admissions and Intensive care unit admissions become more frequent. Certain parameters can predict a greater likelihood of death within a year:decrease in six-minute walk distance of 50 meters, change toward a very sedentary lifestyle, change toward feeling upset or downhearted, increase in arterial tension of carbon dioxide of >3 mmHg, or decrease in arterial tension of oxygen by >5 mmHg[4] .

Palliative care

Palliative care is interdisciplinary care focused on the relief of suffering and improving quality of life[5] . Very often, palliative care is equated with end of life care (EOLC), which is just one aspect of palliative care. When there is evidence that palliative care approach can provide good symptom control and improve quality of life[6,7,8,9,10] ,why not incorporate it early into the disease trajectory?

Palliative care can address difficult to control symptoms, discuss goals of care (GOC) and provide continuity and coordination of care[11] . Clinicians who are looking after these patients on a daily basis can easily incorporate supportive care skills into their practice and involve palliative care specialists when symptoms become complex like intractable dyspnea, pain; complex depression, anxiety, grief or existential distress. Palliative care specialists can also support on difficult communication with patients and family members, and provide guidance and support on ethical issues to the treating physicians. It may be delivered across health care settings, including in the home, long-term acute care facilities, acute care hospitals, and outpatient clinics[12] .Palliative care and hospice care differs in the aspect that palliative care is provided along with curative therapy and hospice care is focused on end-of-life care (EOLC) (Figure 1).

Indications for palliative care consultation

Criteria for palliative care assessment provides guidelines for clinicians when to consult specialty palliative care team (Table 1)

Professor & Head, Department of Pain and Palliative Medicine Amrita Institute of Medical Sciences, Kochi
nair.sobha@gmail.com

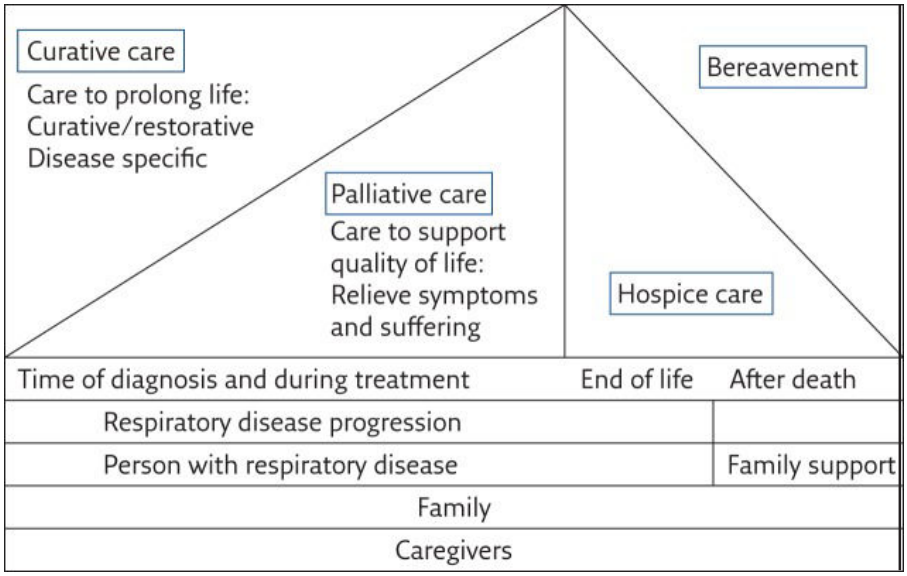

Figure 1 - Model of Palliative Care for Respiratory disease. Adapted from Narsavage et.al, 2017

Table 1 – Criteria for a palliative care assessment / referral

Limited options for treatment
Physical symptoms, such as pain, dyspnea, or cough, that are refractory to conventional management
High symptom burden or distress score
Uncertainty as to prognosis or disease trajectory
Severe or multiple co-morbid conditions
Request for hastened death
The surprise question " you would not be surprised if the patient died within 12 months or before adult-hood"
Frequent admissions (eg: more than one admission for same condition within several months)
Admission prompted by difficult to control physical or psychosocial symptoms (eg: Moderate to severe symptom intensity for more than 24 to 48 hrs)
Complex care requirements (eg: functional dependency, complex home support (ventilator, antibiotics, feedings)
Decline in function, feeding intolerance, or unintended decline in weight (eg: failure to thrive)
Home bound
Older patient, cognitively impaired with fracture
Metastatic or locally advanced incurable cancer
Long term oxygen therapy (LTOT)
Chronic mental illness
Unresolved grief or multiple prior losses
No discussion of long term care goals / goals of care (GOC)

Adapted from Reinke et.al, 2018 and Levy et.al, 2012 -NCCN Guidelines Version 2.2012, Palliative Care

Symptom burden

Among chronic lung diseases, COPD is one of the leading causes of death world over[13] . Breathlessness, fatigue, cough, and pain are frequently reported in patients with COPD and typically increase as their degree of airflow limitation advances[14] . Anxiety and depression are common and significantly impact patients' quality of life. Anxiety ranges from 20% in patients with stable COPD to greater than 75% in patients with se-vere airflow limitation, which may be related to their degree of breathlessness. Depres-sion averages 40% in all stages of COPD and is greater than 60% in those requiring supplemental oxygen [15].

Symptom management

Refractory dyspnoea is common and has to be treated. By the time dyspnoea becomes refractory, clinicians would have exhausted all options including, short acting bronchodilators, long - acting bronchodilators and pulmonary rehabilitation. Apart from optimizing medical management, non-pharmacological measures like keeping the windows and doors open, using fans, humidifying the air etc., might relax the patient. Opioids and using oxygen if there is hypoxia form the main stay of symptom palliation in intractable dyspnoea[16] . Explanations about chronic dyspnoea can be a trigger point for referral to palliative care team[17] . Non- invasive ventilation (NIV) can also be used as a palliative measure when patients and families have chosen to forego all life support and receive comfort measures only[18] .

Oral morphine can be used safely for breathlessness. In an opioid naïve patient, oral morphine can be started in 2.5 mg doses three times a day (TID). It can be titrated up to 5 mg TID or higher if tolerated. For immediate effect, Intravenous injections of 1.5 mg TID can be started and if required made into a continuous infusion over 24 hours. The doses can vary from 10 mg to 30 mg in 24 hours depending on patient need 19. Opioids should always be accompanied by laxatives to prevent constipation. For opioid induced constipation a combination of a stimulant laxative (Senna/bisacodyl) with or without a stool softener (docusate), is recommended 20. Methyl naltrexone bromide, a peripherally acting opioid antagonist is found to be very effective in the management of OIC, especially when given subcutaneously[21].

For patients with dyspnoea accompanied by anxiety, benzodiazepines can be used as adjunctive therapy[22]. Benzodiazepines can be added to opioids, without the risk of respiratory depression[23] . Short acting benzodiazepines like midazolam intravenously(IV) or subcutaneously(S/C)), intermediate acting lorazepam (oral, sublingual (S/L) or IV), or long-acting diazepam (oral, sublingual (S/L) or IV), can be used with optimum results[24] .

Fatigue is an underreported and undertreated symptom in chronic serious illnesses [25]. Systemic glucocorticoids (eg: Dexamethasone 4mg OD), are often used to treat fatigue in palliative care patients. This can be short term and kept to a minimum dose, as long term use of systemic glucocorticoids can increase morbidity and mortality in chronic lung diseases[26].

Cough, sputum production and hemoptysis can add to patients' and caregivers' distress. Diagnostic evaluation is usually the first step, but if it is not consistent with goals of care, symptom management can be adopted. Opioids can be effective for in-tractable dry cough. Morphine, codeine, and dextromethorphan are used to relieve dry cough in a much smaller dose than their regular analgesic dose . Productive cough might require antibiotics and or mucolytics[27]. There are case reports on the use of inhaled tranexamic acid for non-massive hemoptysis with good effect[28] . Massive hemop-tysis might trigger palliative sedation with midazolam (0.2 mg/kg intravenously or subcutaneously) with 5 mg increments every five minutes, until sedation is achieved. Some patients who are used to benzodiazepines might need Phenobarbital (25-100mg /hr) for sedation[29].

Advance Care Planning

Advance care planning (ACP) is defined as "planning for and about preference-sensitive decisions often arising at the end-of-life"[30]. ACP enables individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and health-care providers, and to record and review these pref-erences if appropriate. It is an iterative process and occurs longitudinally in the health care worker's professional relationship with the patient and his family[31].

Goals of Care

Establishing goals of care is an important part of ACP. Each patient might differ in their definition of living well. Some of them would want mechanical ventilation and some of them would prefer to be at home with their family and friends. Care should be provided according to their informed wishes. Establishing goals of care is an opportunity for the clinician to explore patients' expectations, hopes and fears[32]

.

Care giver burden in chronic pulmonary diseases

Majority of care givers in India are family members of patients. As very few can afford a professional caregiver, family members automatically don the role of a caregiver. When the patient reaches an advanced stage, the burden of the caregiver increases (physical, emotional, social and financial). Carers of patients with COPD report anxiety, depression, fatigue, strain, social isolation, uncertainty, confusion, powerlessness, help-lessness, loss of freedom, relationship difficulties, loss of intimacy, psychological dis-tress, resentment, sleep disturbance, guilt, and boredom[33]. It is the health care worker's responsibility to assess the burden of the care giver, bring it to the notice of all family members and ease the burden with the help of other family members and support groups[34].

End of Life Care (EOLC)

Health care professionals should be trained to identify end of life care in patients with chronic pulmonary diseases even when prognostication is very difficult in patients with COPD[30]. Certain guiding principles should be followed in prescribing for symptom management in EOLC. Unnecessary medications can be stopped. Patients might not be able to take medications orally as swallowing becomes impaired . Alternative routes like sublingual, intravenous,subcutaneous and if needed naso-gastric route etc., can be adopted. Dyspnoea, increased oro-pharyngeal secretions, delirium, agitation, and pain are common symptoms during end of life[35]. Opiates should be given to treat dyspnoea during end of life[36]. Antipsychotic medications like Haloperidol can be given for terminal delirium[37]. Benzodiazepines like midazolam can be added for terminal agitation because of their potentially sedating effects [35].Increased oropharyngeal secretions get collected in the hypopharynx as patients lose their ability to swallow. It makes a gurgling noise (death rattle) when patients breathe. It can be controlled by manual suction, hyoscine butylbromide or glycopyrrolate with good effect[38].

Palliative sedation

In patients with severe, refractory agitation, palliative sedation may be considered. Palliative sedation is defined as the intentional lowering of awareness toward, and including, unconsciousness for patients with severe and refractory symptoms. It should be considered only when symptoms do not respond to alternative therapies. A combination of haloperidol, midazolam and morphine can be used as a continuous infusion (mixed in the same syringe) to address different symptoms and to achieve palliative sedation [39].Some patients require Phenobarbital for optimum sedation[29].

Summary

Palliative care can benefit patients and their families suffering with chronic pulmonary diseases. The primary goal of palliative care is to improve quality of life of the patient and his or her family by addressing physical and emotional symptoms. While patients with chronic lung disease have a gradual decline, the trajectory can change abruptly. Advance care planning, setting goals of care, long term care plan and communication regarding end of life are essential. Dyspnoea is the main symptom in advanced lung disease that can be addressed with systemic opioids, irrespective of the underlying lung disease. Palliative treatment of other symptoms like cough, hemoptysis and symptoms during end of life are to be given to provide excellent patient centered care and to maintain quality of life for patients.

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Absolute Eosinophil Count as a marker to differentiate COVID-19 from other short febrile illness

Nair C Sharada[1], Ravi Nivya[2], Padmanabhan Arjun [3] , Nair Sanjeev[4], K A Ameer

Abstract

Purpose: Peripheral blood routine examination results are often abnormal in Covid-19. This study aimed to determine whether absolute eosinophil count can be used as a marker to differentiate covid-19 from other short febrile illness

Materials and Methods: This was a single-center retrospective descriptive study which studied 1000 laboratory confirmed Covid-19 patients and 300 patientswith non-Covid short febrile illness. The peripheral blood routine examination results and relevant demographic parameterson the first day of hospital visit for both groups; and the clinical disease severity category assigned to each patient in the Covid-19 group were obtained from the hospital electronic medical records and analysed at the end of the study using appropriate statistical tools.

Results: The median AEC was 55 cells/mm^3 (13.2-140.4) and 167.57cells/mm^3 (83.6-247.4) in the Covid and non-Covid groups respectively ($p < 0.001$).The median NLR was 2.6 (1.5-5.3) and 2.7 (1.9-4.2) in the Covid and non-Covid groups respectively ($p = 0.689$).Upon comparing mild, moderate and severe clinical disease severity, median AEC was lowest and median NLR was highest in the severe category ($p< 0.001$)

Conclusion: A low AEC may help differentiate Covid-19 infection from other short febrile illness when used in conjunction with clinico-radiological features. An initial low AEC and high NLR can predict increased clinical disease severity.

Keywords:

COVID-19, Eosinophils, Neutrophil-Lymphocyte ratio, Disease severity

Introduction

Coronavirus disease (Covid-19) is an infectious disease caused by a newly discovered coronavirus SARS-CoV2. Covid-19 infection is confirmed using molecular tests /rapid immunochromatography antigen tests approved by the World Health Organization. However, the low sensitivity of these tests combined with the long waiting time for chest imaging frequently results in a delay in diagnosis and hence quarantine and/or therapeutic decisions are often not made in time.[1] Various studies worldwide noted that laboratory biomarkers like absolute eosinophil count (AEC) and neutrophil lymphocyte ratio (NLR) can be used to effectively triage patients at fever clinics and to differentiate suspected Covid-19 patients from those with other short febrile illness.[2,3]

The Primary Objective of this study was to determine whether there is a statistically significant difference in the peripheral absolute eosinophil count (AEC) between Covid-19 and non-Covid 19 infection. **Secondary Objective** was to determine the association of AEC and NLR with clinical disease severity in adult Covid-19 infection.

Materials and Methods

Study design, setting and population:

This was a single center record based descriptive study conducted at a tertiary care hospital in Thiruvananthapuram, Kerala. We retrospectively collected anonymized records of 1000 consecutive outpatients and inpatients aged more than 18 years, from December 2020

1- DNB resident- 2nd year

2- DNB resident- 1st year

3-Sr. Consultant and Group Coordinator

Department of Respiratory Medicine, Kerala Institute of Medical Sciences, Anayara P.O, Trivandrum – 695029, Kerala, INDIA

4-Associate Professsor, Department of Respiratory Medicine, Govt. Medical College, Trivandrum

5-Senior Consultant and Academic coordinator, Department of Respiratory Medicine, Kerala Institute of Medical Sciences, Anayara P.O, Trivandrum – 695029 Kerala, INDIA

Corresponding author:

1.Padmanabhan Arjun ,Sr. Consultant and Group Coordinator, Department of Respiratory Medicine, Kerala Institute of Medical Sciences, Anayara P.O, Trivandrum – 695029, Kerala, INDIA, dr.p.arjun@gmail.com

to February 2021, who were diagnosed as COVID-19 with a molecular assay (RT-PCR/chip-based RT-PCR/ cartridge based PCR) or a rapid immunochromatography antigen assay were included in the Covid positive group. During the same study period, anonymized records of 300 consecutive outpatients and inpatients aged more than 18 years, who had symptoms and signs suggestive of Influenza like illness but tested negative for Covid-19 as per molecular assay (RT-PCR/chip-based RT-PCR/ cartridge based PCR) or a rapid immunochromatography antigen assay were included in the non-Covid group.These patients were under our follow-up and treatment, and were evaluated, in detail with viral panels, repeat testing with either RT-PCR or antibody test and CT chest scans when appropriate. Only those who were thought to be as non-Covid short febrile illness by our hospital infectious diseases team, were taken as controls. Exclusion criteria were patients with incomplete electronic medical records data and patients who were on any short term or long term systemic steroids. This retrospective study was approved by our institutional review board. As the study posed no potential risk to patients and since the data extraction was anonymized, removing patient identifiers, informed consent was waived. The confidentiality of patients was observed.

Data collection:

Relevant parameters obtained from our electronic medical records were age,sex,and presence of any comorbidities. Laboratory parameters studied were serum total and differential leucocyte count, neutrophil lymphocyte ratio (NLR) and absolute eosinophil count (AEC) on the first day of hospital visit. For the Covid positive group, the clinical disease severity category (mild/moderate/severe) that was assigned to each patient at the time of admission according to the institutional COVID-19 treatment guidelines which was adopted from the COVID-19 management protocol guidelines issued by the All India Institute of medical sciences, New Delhi [4]and the COVID-19 interim treatment guidelines by the Kerala state government[5], was also noted. (Table 1) Patients who worsened clinically during their hospital stay were recategorized accordingly and the highest clinical disease severity category assigned to each patient at the time of discharge/ death was noted.

Study outcomes:

1. The median AEC in the Covid and non-Covid groups and to determine whether there is a statistically significant difference in the median AEC between Covid-19 and non-Covid infection.
2. Proportion of patients with an absolute eosinophil count (AEC) < 100 cells/mm^3 in the Covid and non-Covid groups.
3. Association of the median AEC and median NLR with the clinical disease severity category in the Covid group.
4. To plot a ROC curve and determine a cut off AEC that can differentiate Covid-19 and non-Covid-19 infection.

Statistical analysis:

The data was collected into MS Excel and analysed at the end of the study using statistical software Epi Info version 7.2.2.6, Centers for Disease Control and Prevention (CDC) Atlanta, Georgia (US) and an ROC curve generated using the web-based tool, easy ROC.[6]Results on categorical measurements were expressed in number (%) and results on continuous measurements were presented in mean (± standard deviation) or median (interquartile range). Comparison between categorical variables were assessed using 2 tailed÷2 test; and between quantitative variables were assessed using the Student t test or Kruskal-Wallis test as appropriate. A p value of less than 0.05 was considered to be statistically significant. A ROC curve was plotted and Youden index method was used to determine a cut off AEC that can differentiate Covid-19 and non-Covid-19 infection.

Results

The Covid group consisted of 1000 patients and the non-Covid group consisted of 300 patients. The mean age in the Covid group and the non-Covid group was 51.06 years (± 17.55) and 48.92 years (± 18.64) respectively. 55.3% of the Covid positive group were males whereas 57.3% of the non-Covid group were females. The most common comorbidity in both groups was diabetes mellitus.The major difference in the two groups was in the higher proportion of females and cancer as a comorbidity in the non-Covid group. (Table 2).

Age – expressed as mean + Standard deviation and compared using student t test.

Other variables expressed as number and percentage and proportions compared using chi-square test.

The median AEC was 55 cells/mm^3 (13.2-140.4) and 167.57cells/mm^3 (83.6-247.4) in the Covid and non-Covid groups respectively ($p < 0.001$). The median neutrophil lymphocyte ratio (NLR) was 2.6 (1.5-5.3) and 2.7 (1.9-4.2) in the Covid and non-Covid groups respectively ($p = 0.689$) 65.7% patients in the Covid group had an abso-

Table 1: Clinical disease category as per our institutional Covid-19 treatment guidelines

MILD	MODERATE	SEVERE
Upper respiratory tract symptoms without fever/shortness of breath/hypoxia.	Any one of below:- Fever- Shortness of breath with respiratory rate 22- 30/min and SpO2 90-94% room air	Any one of below:- Respiratory rate > 30/min -SpO2 < 90% room air

Table 2. General characteristics of the patients who participated in the study

	Covid n=1000		Non-Covid n=300		P value
Age(yrs)	51.06	±17.55	48.92	±18.64	0.068
Female sex	447	44.7%	172	57.3%	<0.001
Asthma	44	4.4%	8	2.7%	0.178
Coronary artery disease	111	11.1%	37	12.3%	0.562
Cancer	41	4.1%	68	22.7%	<0.001
Chronic Kidney Disease	75	7.5%	14	4.7%	0.086
COPD	13	1.3%	5	1.7%	0.636
Chronic Liver Disease	37	3.7%	12	4.0%	0.815
Dyslipidemia	92	9.2%	18	6.0%	0.079
Diabetes mellitus	353	35.3%	95	31.7%	0.241
Hypertension	312	31.2%	59	19.7%	<0.001

Table 3. Blood counts in the patients recruited in the study

	Covid n=1000		Non-Covid n=300		P value
Total leukocyte count	6400	(5000-8800)	7850	(6600-9700)	<0.001
Neutrophil count	3895.3	(2655-6076)	4934	(3805.6-6541.8)	<0.001
Neutrophils %	63.3%	(51.1%-75%)	64.9%	(56.7%-73.4%)	0.051
Lymphocyte count	1488	(975-2035.5)	1872.2	(1360.4-2514.9)	<0.001
Lymphocyte %	24%	(14%-34.2%)	24.3%	(17.4%-31.3%)	0.993
Eosinophil count	55	(13.2-140.4)	167.57	(83.6-247.4)	<0.001
Eosinophil%	0.9%	(0.2%-2.1%)	2.1%	(1.1%-3.2%)	<0.001
Neutrophil Lymphocyte Ratio	2.6	(1.5-5.3)	2.7	(1.9-4.2)	0.689

lute eosinophil count of < 100cells/mm^3 as opposed to only 29% in non-Covid group. 10.1 % of the Covid positive patients presented with 0 eosinophil count. (Table 3). Values expressed as median (inter-quartile range). Unit of blood cell counts:cells/mm^3

Test of significance – Mann-Whitney U test

A ROC curve was plotted to determine the ability of AEC to differentiate between Covid and non-Covid with an area under the curve of 0.722 (95% CI: 0.691, 0.754) and p value of 1.37. Using Youden index cut off method, an AEC of 96 cells/mm^3 had a sensitivity of 64.7% and specificity of 72% to differentiate Covid from non-Covid infection. (Figure 1)

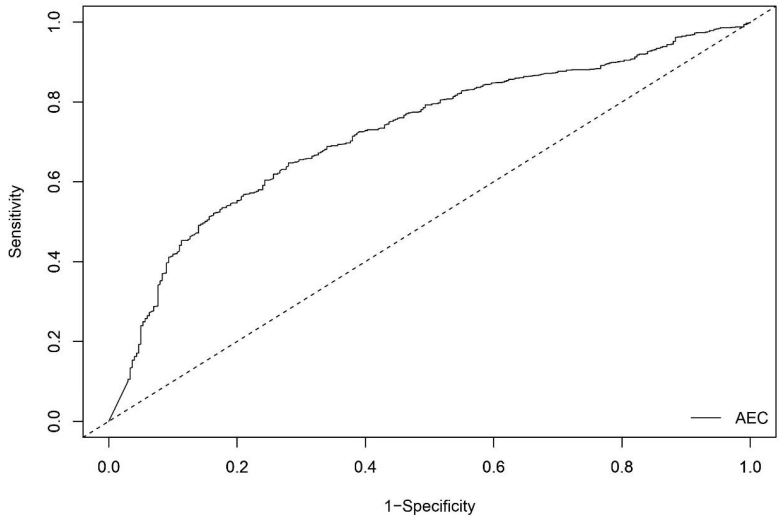

Figure 1: ROC curve to determine a cut off AEC that can differentiate Covid-19 and non-Covid-19 infection.

Upon comparing each clinical disease severity category, the median AEC was 81.2 cells/mm^3 (28-175) in the mild category, 57.95 cells/mm^3(17.4-133.4) in the moderate category and 8.4 cells/mm^3(0.53-55) in the severe category (p< 0. 001). The median NLR was 1.8 (1-3.8) in the mild category, 2.4 (1.2-6) in the moderate category and 8 (3.1-17) in the severe category (p< 0. 001).

Discussion

Eosinophils are circulating and tissue-resident leucocytes that have proinflammatory effects in a variety of diseases. Recently, they have been shown to have immunoregulation and antiviral activity also. The peripheral absolute eosinophil count has a normal range of 100-400 cells/mm^3 and contribute to 1-3% of the total blood leucocyte pool.[7]

Eosinopenia, defined as a reduced eosinophil count in peripheral blood; has long being identified as a good diagnostic marker of most blood stream infections.[8] A reduced peripheral eosinophil count has also been observed during Covid-19 infection.[7,9]The pathophysiology for eosinopenia in Covid-19 remains unclear and is possibly multifactorial. Various hypotheses include reduced eosinophilopoiesis, inhibition of eosinophil release from the bone marrow and/or direct eosinophil apoptosis stimulated by type 1 Interferon released during the acute infection.[7,9]

Similarly, the neutrophil lymphocyte ratio (NLR) is an established inflammation marker that can reflect systemic inflammatory response. The NLR value has been noted to be increased significantly in patients with severe Covid19 disease and NLR hence may help in early prediction of Covid-19 patients who are likely to develop critical illness.[2]

Absolute eosinopenia was variably defined in worldwide studies and does not have a universal definition. A reduced absolute eosinophil count was defined in our study as <100 cells/mm^3 which is the cut off used in most eosinophil related studies.[10]

In our study, the median absolute eosinophil count was lower in the Covid group as compared to the non-Covid group and this difference was found to be statistically significant.Du et al.[11] reviewed 85 fatal cases of Covid-19 and noted that 81% of the patients had absolute eosinophil count <0.02 × 10^9 cells/L (20 cells/mm^3) at the time of admission.Li et al.[3]noted that eosinopenia and

elevated highly sensitive C-reactive protein (e"4.0/mg/L) can effectively triage Covid-19 patients from other patients attending the fever clinic with a positive predictive value at 72.7%.Khourssaji M et al.[12]observed that eosinopenia, high NLR, as well as high serum CRP,D-dimer, ferritin was consistently found in Covid-19 patients.However, in our study, there was no statistically significant difference in the median NLR between the Covid and non-Covid groups.

Both AEC and NLR in our study, showed a significant association with the clinical disease severity of Covid-19. The median AEC was lowest in the severe category and the median NLR was highest in the severe category. Huang et al.[13] categorized Covid-19 patients into eosinopenia (AEC on admission < 20 cells/mm^3) and non-eosinopenia groups and observed a significantly higher ICU admission rate in the eosinopenia group than in the non-eosinopenia group (51 vs. 9%, p< 0.001). Yan et al.[14] noted that the eosinophil levels were significantly lower in patients with critical disease, when compared to those with moderate disease andalso observed that a progressive decline of eosinophil count was independently associated with mortality. They also noted that the eosinophil level significantly and positively correlated with D-dimer and platelet count whereas it inversely correlated with serum urea, creatinine, aspartate aminotransferase, lactate dehydrogenase, and creatine kinase.

Ciccullo et al.[15]noted that a higher NLR at the time of hospital admission was associated with a more severe outcome. They observed that a NLR of >4 was a predictor of ICU admission. A systematic review and meta-analysis by Xiaoming Li et al.[16]showed that the NLR has a good predictive value on disease severity and can also predict mortality in patients with Covid-19.

Strengths of the study:

This is the first study of its kind from South India. We included a large sample size of 1000 patients who tested positive for Covid-19. The diagnosis and blood routine investigations were standardized**.**

Limitations of the study:

AEC and NLR on the day of hospital admission for each patient was taken for our study and serial change in AEC and NLR throughout the course of the disease was not studied. Blood counts can change as the days progress and each of our patients may have been in different stages of illness as per days from symptom onset at the time of hospital admission.

The statistical association between AEC and NLR with clinical disease category was not adjusted for confounders like age, sex and comorbidities in the present study.

Conclusion

A low AEC at the time of initial presentation can be used to help segregate suspected Covid-19 patients from other short febrile illness. It can be used as a marker in resources limited situations where there is a poor/lack of access to RT-PCR tests and when there isa significant delay to obtain results.Also, a low AEC and/or a high NLR at baseline can aid in early prediction of severe clinical disease in Covid-19.

However, it is to be noted and stressed that triaging or segregating suspected Covid-19 patients from other short febrile illness as well as the prognostication of Covid-19 illness, must always be based on a combination of clinical symptoms, radiological features and laboratory parameters and not just based on blood counts alone.

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Eosinophil count in COPD – Do we need different cut-offs for our population?

Kiran CR[1], K Anitha Kumari[2], Sanjeev Nair[3], Thomas George P[4]

Abstract

Background: Blood peripheral Eosinophil count in COPD patients is increasingly being considered as a biomarker in COPD and is now being included in major guidelines to guide treatment, particularly in the use of inhaled corticosteroids.

Objective: To estimate the peripheral blood Absolute Eosinophil Count (AEC) in COPD patients attending the Pulmonary Medicine OPD, Government Medical College, Trivandrum.

Methodology:A cross-sectional study was done recruiting 145 COPD patients consecutively. Patients were interviewed with a structured questionnaire and their AEC was calculated by the standard haematological method. Analysis was done with EpiInfo version 7.

Results:145 Patients with COPD were recruited for the study and 112 MDR TB patients served as control. The mean AEC in COPD patients was 490 ±641. The AEC was significantly higher in the COPD group compared to another patient population in the same hospital represented by the Multi-Drug Resistant Tuberculosis (MDR TB) group (median of 469 for COPD vs. 231 for MDR TB;p value< 0.001). Among the physiological variables, a higher BMI was associated with a greater Eosinophil count.

Conclusion:64.83% of COPD patients had an AEC greater than 300, which was the cut off recommended by GOLD guidelines for the use of inhaled cortico- steroids. Using the same value as in Western guidelines can lead to a rather liberal use of steroids in the Indian population, with its accompanying side effects.

Key words: Pulmonary Disease, Chronic Obstructive;Eosinophilia , India, Kerala

Introduction

Absolute Eosinophil Count (AEC) in peripheral blood is a useful investigation that guides treatment in many diseases like ABPA, Eosinophilic lung diseases and parasitic lung diseases to name but a few. Blood peripheral Eosinophil count in COPD patients is increasingly being considered as a biomarker in COPD and is now being included in major guidelines to guide treatment, particularly regarding the use of inhaled corticosteroids. AEC is now considered a major biomarker in COPD. However, the cut-offs for AEC in guidelines and other studies, including the GOLD guidelines are at 300 for all COPD patients and 100 for COPD patients with recurrent exacerbations.[1] GOLD 2019 recommended AEC as guidance for starting inhaled steroids in COPD group D patients, with those patients with eosinophil ≥ 300 being eligible for the same. In general practice in India, such levels of counts have often been found to be common, leading to the feeling that the AEC of cut-offs of the GOLD guidelines may not be appropriate for the Indian population.It is in that context that this study was conceived to address the lack of data regarding AEC in Indian COPD patients. The pattern of COPD in Indian patients is significantly different from the western population. Indian patients contain a greater population of females, non-smokers and malnourished patients. The contribution of indoor and outdoor pollution is also greater[2]. At the other end of the malnutrition spectrum, India is the global capital of lifestyle diseases including diabetes, hypertension, and morbid obesity. Unlike TB the treatment of COPD in India is hampered by the absence of a comprehensive national guideline. This has led to a rather empirical use of inhaled and systemic cortico-steroids. It has been seen that there is often use of

1 - Assistant Professor, Department of Pulmonary Medicine, Medical College, Thrissur
2- Professor & HOD, Department of Pulmonary Medicine, Medical College, Trivandrum
3- Associate Professor, Department of Pulmonary Medicine, Medical College, Thrissur
4 -Professor & HOD, Department of Pulmonary Medicine, Medical College, Thrissur
Corresponding author:
Kiran CR, Assistant Professor Department of Pulmonary Medicine, Medical College, Thrissur.
kirancrtvm@gmail.com

ICS in more patients than those on bronchodilators.[3] While this was thought to be an overuse of ICS, it might be justified as per the GOLD guidelines if the AEC of these patients were high. Hence we took up the study to study the distribution of AEC and how it varies with respect to the risk factors of COPD which are more common in India.

Methodology

This study was conducted in the department of Pulmonary Medicine, Government Medical College, Thiruvananthapuram. Ethics committee clearance was obtained on 19/12/2017 with IEC number 15/11/2017/ MCT from Government Medical College, Thiruvananthapuram. A total of 145 COPD patients were recruited for the study prospectively, from both the IP and OP, all of whom were selected consecutively. 112 patients with MDR-TB from the same district were also selected consecutively for the study, who served as the control group for analysis of Absolute Eosinophil Count (AEC).

Patients in whom COPD was diagnosed by the presence of typical symptoms, history of exposure to noxious particles and having an FEV_1/FVC ratio less than 0.7 were included in the COPD group. Patients with Asthma COPD overlap and those who had already been on inhaled steroids for more than a year, or on other immunosuppressants that can affect the Eosinophil count were excluded from this group. The Multi-Drug Resistant Tuberculosis(MDR TB) group, which served as the control group, included those who had a microbiologically confirmed diagnosis of MDR TB. Patients excluded from this group were, those with co-existent COPD and other diseases that could affect AEC. A structured questionnaire was used to collect relevant data from all patients. Absolute Eosinophil Count was determined by direct counting from the haemocytometer after appropriate staining.

Results

The study focussed mainly on COPD patients. The mean age of the COPD group was 65.56 ± 15 years. The median age was 65 with IQR 60 to 71. Most of the patients were males (80.00%). 40.20% of patients had a smoking index of more than 800. 48.28% of patients had atopic symptoms. Group D COPD made the largest group among these patients(n=60, 41.38%), followed by group B (n=40, 27.59%). Group A (n=23, 15.86%) and group C (n=22, 15.17%) were less common. The general characteristics of this group are given in table 1 below.

For comparison, we added an MDR-TB group. The mean age of this group was 44.98 ± 28 years. The median age was 47.50 years with an IQR of 34 to 57 years. This group comprised of 24 males (21.43%) and 88 females (78.57%)

The mean AEC in the COPD group was 490.45 ± 641 with a median of 469 (IQR 245 to 671). A maximum number of patients had AEC ranging from 200 to 300 with the numbers decreasing on either side of this peak. The mean AEC in the MDR TB group was 330.15±638 with a median of 231 (IQR 115 to 462.50). The highest proportion of patients (25%) had AEC less than 100 and the distribution of patients followed a decreasing trend throughout from here. The distribution of AEC is given in figure 1 below.

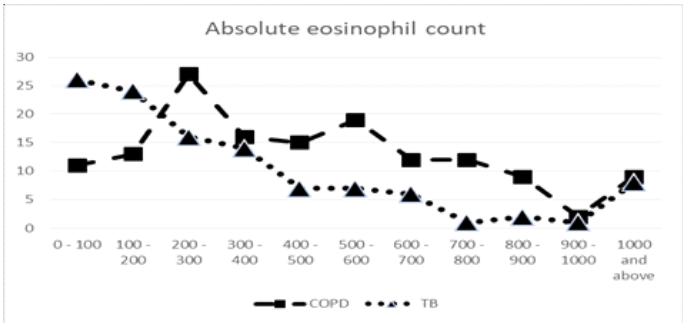

Figure 1: Distribution of AEC in COPD and TB groups

The difference in mean in the two groups was statistically significant with a p-value <0.005.

The cumulative percentage of patients in each COPD group were assessed, based on increasing Eosinophil count, and the results are shown in Table 2.

Variables compared between the high and low eosinophil groups in COPD patients included age, sex, BMI, smoking index greater than 800, history of deworming and COPD groups. In patients with AEC > 300, the proportion of patients with BMI < 18.5 kg/m^2 was significantly higher, with a p-value of 0.029. None of the other variables showed any significant difference. (Shown in table 3.)

Discussion

This study estimated the eosinophil levels among patients with COPD presenting at a tertiary care centre in South India. Eosinophil directed therapy is now an accepted way of managing COPD. Improved care for COPD is important as among all the leading causes of death, COPD is the only disease that continues to increase in prevalence.[4]Since COPD is the result of multiple pathological processes, each involving different cells and inflammatory mediators[5]. The common pattern of inflamma-

Table 1. General characteristics of the study population

Character	N	Proportion	Percentage
Age >65	145	70	48.28%
Males	145	116	80.00%
Atopic	145	70	48.28%
SI>800	102	41	40.20%
BMI<18.5	145	29	20.00%
Age of onset< 60	145	51	35.17%
COPD Group A	145	23	15.86%
COPD Group B	145	40	27.59%
COPD Group C	145	22	15.17%
COPD Group D	145	60	41.38%

Table 2. Eosinophil counts in the various groups of COPD patients

	AEC groups					
	More than 100		More than 300		More than 500	
COPD GROUP	N	Percentage	N	Percentage	N	Percentage
Group A (n=23)	23	100.00%	17	73.91%	7	30.43%
Group B (n=40)	35	87.5%	21	52.50%	15	37.50%
Group C (n=22)	22	100.00%	15	68.18%	11	50.00%
Group D (n=60)	54	90.00%	41	68.33%	30	50.00%
TOTAL	134	92.41%	94	64.83%	63	43.45%

Table 3. Factors associated with eosinophil count more than 300

		AEC<300		AEC>300		p value
		N	Percentage	N	Percentage	
Age	<65	29	56.86%	46	48.94%	0.388
	>65	22	43.14%	48	51.06%	
Sex	Male	41	80.39%	75	79.79%	0.556
	Female	10	19.61%	19	20.21%	
BMI	<18.5	5	9.80%	24	25.53%	0.029
	>18.5	46	90.20%	70	74.47%	
Smoking Index	<800	21	58.33%	45	63.38%	0.675
	>800	15	41.67%	26	36.62%	
Atopy	Present	27	52.94%	48	51.06%	0.0863
	Absent	24	47.06%	46	48.94%	
Deworming	Not done	25	62.50%	46	54.76%	0.443
	Done	15	37.50%	38	45.24%	
COPD Groups	C & D	26	50.98%	38	40.43%	0.381
	A & B	25	49.02%	56	59.57%	

tion in COPD is neutrophilic. eosinophils are important as a defence against microbes.[6] Its exact role in the development of COPD has also not been fully understood. Eosinophilic inflammation is seen in 20 to 40 % of COPD patients.[7-9]This inflammation is similar to the type 2 inflammation seen in asthma. Because of its role in lung defence, there is a risk for the development of pneumonia when eosinophils are suppressed by steroids, particularly if the Eosinophil count was low, to begin with. Recently, significant eosinopenia has been observed in COVID-19 patients albeit with no effect on survival.[10]

Recent GOLD guidelines (2019) advocated the use of AEC to start inhaled steroids. This could be useful even in the Indian context as it is a simple blood investigation that can be done in most laboratories. The blood AEC corresponds well to the sputum AEC and thereby acts as a good surrogate.[11,12]. There are studies that showed that patients with AEC $\geq$ 300 or a differential count of eosinophils $\geq$ 2% had a greater than normal risk of suffering exacerbations[13,14]. There are also studies that prove that a high AEC indicates a better response to steroids[7,15,16]. Alternatively, some studies prove that the use of inhaled steroids in patients with AEC $\leq$ 100 is associated with a greater risk of pulmonary infections.[16] Eosinophilia is a treatable trait in COPD. Similar to asthma, reduction of eosinophilia, even with drugs like Mepolozumab translates to a reduction in exacerbations.[17] Based on these study results, GOLD guidelines recommended a cut-off of 300 of AEC for prescribing inhaled corticosteroids (100 in frequent exacerbators). However, there was considerable apprehension among experts in India that these cut-offs may not be ideal for an Indian COPD patient.

COPD is a disease that is underdiagnosed in India, even more so in females than in males. The largest study done in India regarding airway diseases, the "INSEARCH" study found a prevalence of 3.49% for chronic bronchitis, which is much lower than the global prevalence rates.[18] The prevalence of smoking in men, is 19.0% and for women is 2.0% (GATS India report 2017).The incidence of smoking in females is much less than in western countries. Exposure to biomass fuels plays a much greater role in causing COPD. This is strikingly more evident in the case of females. Based on these differences, it has been hypothesised by Salvi S, that the Indian COPD patient is significantly different from the western COPD population. Indian patients contain a greater population of females, non-smokers and malnourished patients. The contribution of indoor and outdoor pollution is also greater[2].

These differences indicate that the pattern of inflammation may also be different in India. Studies indicate that exposure to biomass fuel, as well as to air pollution can cause lung eosinophilia[19]. The state of Kerala, where the study was conducted is in the midst of an obesity pandemic. Obesity is a well-known cause of inflammation, especially Eosinophilic[20,21]. Similar to bronchiectasis and asthma, COPD can also manifest allergic bronchopulmonary aspergillosis. This is also another cause of Eosinophilia in COPD patients in India[22]

Some reasons are not related to COPD, which can still cause an elevation of AEC, in the general Indian populace. Their impact on COPD is unknown. The most important among these are parasitic infestations. Most parasitic infestations are more common in tropical countries, including India and they cause significant elevation of eosinophil count. Drugs like NSAIDs and proton pump inhibitors can also elevate Eosinophil counts. Such drugs are available over the counter in India and are commonly overused. The use of herbal remedies is also believed to affect eosinophil counts and other inflammatory markers. Some of these drugs contain alkaloids and other allergenogenic substances that can cause systemic eosinophilia. Genetic predisposition to atopy and high eosinophil count may also have conferred a survival advantage in tropical countries where infections and infestations are much more common.

The current trend in COPD is to avoid inhaled corticosteroids in COPD patients unless there could be a benefit, to avoid the occurrence of pneumonia. Therefore, if the eosinophil counts in Indian patients are higher, using inhaled steroids in patients with AEC $\geq$ 300, (AEC $\geq$ 100 in those with frequent exacerbations) would result in a majority of Indian COPD patients getting inhaled corticosteroids. Most of the studies done on Eosinophilia and mentioned in GOLD were limited to the developed world. What is a "normal" eosinophil count for an Indian COPD patient has not been studied. This study brings out the fact that if the GOLD suggested cut-offs are used in our patients too, then a vast majority of our COPD patients could end up getting inhaled corticosteroids.

The field realities in India are different from what can be anticipated from the guidelines. A study on the current management of COPD patients showed the use of steroids in Indian COPD patients to be much higher than what could be expected.[3] However, if we were to accept that the use of inhaled steroids in patients with

AEC ≥ 300 is beneficial, the observation that -the use of inhaled steroids is high in India; as reported in the previous study may be inadvertently justified since 70% of COPD patients in the population have an AEC>300, permitting a prescription of ICS as per GOLD guidelines. The preference for steroids may have been from physicians observing improvement in their patients. In this context, we would need to evaluate further whether the high AEC in the Indian patient is associated with a benefit when ICS is used in treatment.

The study also attempted to look at the factors that could be associated with higher AEC, and except for BMI none of the other factors was associated with higher AEC. The study could not, however, evaluate other causes which could result in eosinophilia like worm infestations or filariasis, which could be common co-morbidities.

The strengths of this study are that the COPD patients are patients diagnosed by a team of expert pulmonologists following the current guidelines. This study has for the first time brought the range of the blood AEC level in a population of Indian COPD patients.

Limitations of our study

The limitations of the study include the fact that the COPD group was compared to the MDR-TB group which served as the control group. In the ideal scenario, "normal subjects" should have been controls, but this was not operationally feasible, hence MDR TB patients were taken as a surrogate. This was done on the assumption that tuberculosis has very little impact on AEC and would mirror the normal eosinophil count of the general population. However, there are a few studies that indicate that AEC can increase in tuberculosis in rare instances.[23,24] hence the assumption may not hold. A cross-sectional study in the general population was beyond the scope of this study but may be essential to determine what is the "normal" eosinophil count in the Indian population. The other limitation was that we could not evaluate our COPD patients for other causes of eosinophilia which could have co-existed. This could be an area of further research, looking at the proportion of COPD patients with worm infestations and filariasis. All patients in the control group were diagnosed to have COPD based on spirometry findings only. The spirometry findings are not included here as the authors expect to present further analysis including the relationship between AEC levels, spirometry and COPD symptoms as part of a follow-up cohort study. Cases that could be classified as Asthma COPD overlap were excluded, based on the existing GOLD and GINA guidelines at that time. However, it's possible that despite our best attempts some cases of asthma with fixed airway obstruction, or ACO may have made it into the COPD cases group.

Conclusion

The mean eosinophil count in COPD patients was much higher than that of the western population. When we use the GOLD cut off of 300, we find that 64.83% of our population come under the high eosinophil group and therefore eligible for inhaled steroids. The only parameter that correlated with an AEC ≥ 300 was BMI ≤ 18.5. The use of inhaled steroids in all COPD patients with AEC ≥ 300 can be excessive, and lead to adverse effects in many patients. Hence further studies are needed to confirm whether the use of inhaled steroids as recommended by GOLD is beneficial in Indian patients. Cross-sectional studies to determine the Absolute Eosinophil Count in the broader, general population was out of the scope of this study and such studies are also highly recommended as data in this direction is almost non-existent.

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Nil

Conflicts of interest

There are no conflicts of interest

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A pleural based lesion diagnosed with CT chest

Hasha Thankam Somson[1], Jolsana Augustine[2], Melcy Cleetus[3], Divya R[4], Teena Sleeba[5], Rajesh V[6]

Case Summary

A 51-year-old woman with a medical history of systemic hypertension, hypothyroidism and psoriasis, who was planned for Total abdominal hysterectomy with bilateral salpingo-oophorectomy for large uterine fibroid with ovarian dermoid presented to the pulmonary outpatient department to obtain fitness for the surgery.She complained of mild difficulty in breathing and non-productive cough for 3 days. She denied any history of fever, chest pain, loss of appetite or loss of weight. There was no history of exposure to occupational hazards. She was hemodynamically stable and had no significant findings on physical examination.

Chest X-ray- posteroanterior projection (Fig 1) as well as representative images of non contrast enhanced CT chest – mediastinal window and lung window (Fig 2 – a and b) are shown below. What is the diagnosis?

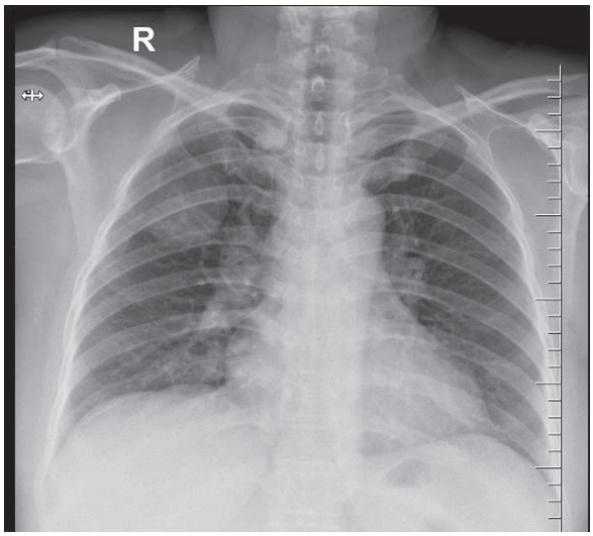

Fig 1 – chest Xray – PA view

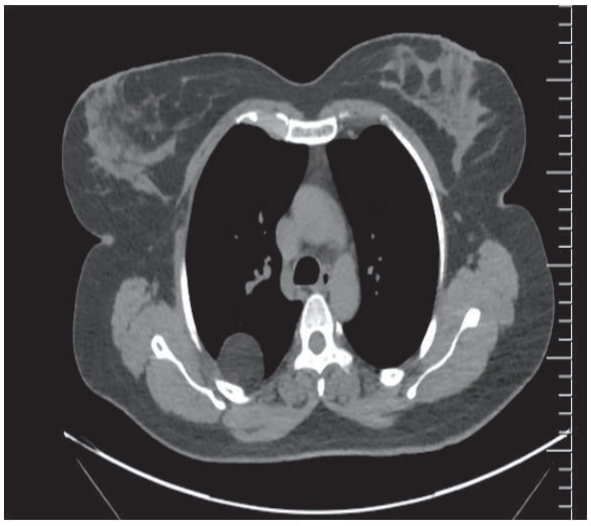

Fig 2a – Non contrast enhanced CT chest – mediastinal window – representative image

Diagnosis

Pleural lipoma

Discussion

Chest radiograph (Fig 1)shows well circumscribed mass lesion in the right upper zone extending into the right midzone with no cavitation, calcification, adenopathy, atelectasis or bony cage involvement. The medial border is very well defined and visible; the lateral border is also distinct but has close proximity to the medial border of scapula. The mediastinal window image of the non contrast enhanced CT shows a pleural soft tissue density lesion in right upper zone posteriorly measuring 3.8 x 3.0 cm. The lesion has homogeneous attenuation with no features to suggest invasion of neighbouring anatomical structures. The lesion exhibits fat attenuation measuring (-90) HU with no rib erosion or scalloping. A contrast enhanced CT was not performed as she had borderline hypertensive nephropathy. No parenchymal abnormalities or mediastinal lesions were identified. Thoracic soft tissue structures and bony cage are unremarkable. The overall appearance is highly suggestive of a pleural lipoma.

Itis not uncommon to come across fat-containing lesions in chest CT imaging. Such lesions may be located at varying locations including the lung parenchyma, air-

1. Observer in Pulmonary Medicine, Rajagiri hospital, Aluva
2. Consultant Pulmonologist, Rajagiri hospital, Aluva
3. Consultant Pulmonologist, Rajagiri hospital, Aluva
4. Consultant Pulmonologist, Rajagiri hospital, Aluva
5. Sr Consultant Radiologist, Rajagiri Hospital, Aluva
6 . Sr Consultant and HOD of Pulmonary Medicine, Rajagiri hospital, Aluva

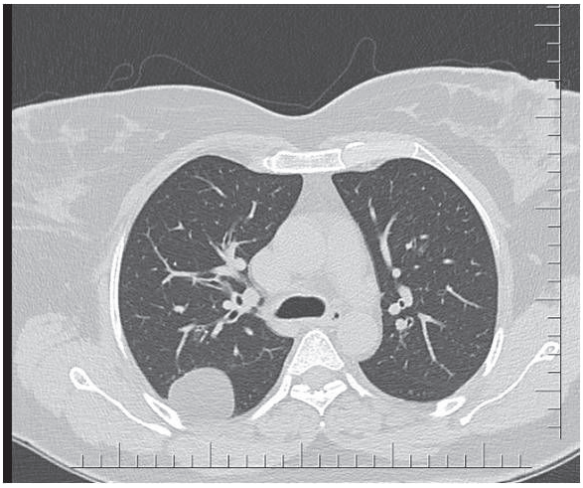

Fig 2b – Non contrast enhanced CT chest – lung window – representative image

ways, mediastinum and accordingly the differential diagnosis varies[1]. Commonest location of intrathoracic fat density lesions is the lung parenchyma and aetiologies include hamartoma, lipoid pneumonia, and lipoma. The typical appearance of endobronchial hamartoma on CT imaging is as a well defined lesion with smooth margins, focal collections of fat and foci of calcification. The differentials of mediastinal fat containing lesions are mediastinal lipomatosis, germ cell tumours, thymolipomas, lipomas, and liposarcomas. Teratoma appears as a heterogeneous mass with soft-tissue, fluid, fat, and calcium attenuation. Cardiac lesions with fat content include lipomatous hypertrophy of the interatrial septum and arrhythmogenic right ventricular dysplasia. Pleural lipomas are described but are uncommon lesions. Herniation of abdominal fat into the thorax is frequently encountered and has several characteristic locations.

Lipomas have a mesenchymal origin and are benign neoplasms. Commonest location of lipomas is in the subcutaneous tissue; however, it is noteworthy that they may be present at any location of the human body. Lipomas arising from the thoracic pleura are exceptionally rare, with a publication in 2020 identifying only 20 cases ever reported in the literature[2]. Lipomas are soft, encapsulated tumours on gross appearance. Clinically and radiologically, they may exhibit slow growth. Lipomas can occasionally arise from the diaphragm also. Pleural lipomas being located distal to vital structures and airways are characteristically asymptomatic. However, they may cause compressive symptoms such as non-productive cough, chest pain, and dyspnoea if they reach adequate size. Huge pleural lipomas have been reported in literature[3].

Pleural and diaphragmatic lipomas appear as soft-tissue density lesions on chest radiographs.Their dimensions vary remarkably on a case-to-case basis. In a chest radiograph, it practically impossible to distinguish a pleural lipoma from a peripheral parenchymal or pleural malignant lesion. A CT scan, on the other hand, is usually sufficient for the diagnosis and typically reveals well-defined nodules with homogenous fat attenuation of approximately -50 to - 150 Hounsfield units. As many lipomas contain fibrous stroma, the density of the lesion may be non uniform and a heterogeneous density lesion does not rule out this diagnosis. It is in such scenarios that distinguishing between a benign lipoma and a well-differentiated liposarcoma proves challenging. This distinction is of utmost clinical relevance, since suspicion of a liposarcoma would necessitate further diagnostic workup with histopathology. Some key differentiating features include uniformly heterogeneous constitution or invasion of neighbouring anatomical structures, which are actually indications to obtain a pathological diagnosis. An additional feature is that CT or MRI demonstrates contrast enhancement in the areas of soft tissue irregularity. On MRI evaluation, pleural lipomas display the same intensity of subcutaneous fat on all sequences and exhibit complete fatty signal suppression on fat-saturation techniques[4]. Due to their broad fibrous septa and margin irregularity, liposarcomas often exhibit focal areas of hypoattenuation on T1-weighted sequences, which is not a feature of lipomas. PET imaging is handy in differentiating lipomas and liposarcomas in challenging scenarios.

The clinician must take into account multiple aspects to decide the management of pleural lipomas including tumour dimension, associated symptoms, and growth rate[5]. In asymptomatic patients with classical radiological findings (having no room for diagnostic confusion), an expectant approach with periodic reimaging would suffice. Rapid growth or development of symptoms would prompt surgical excision for diagnostic and therapeutic reasons. Rapid enlargement need not always signify malignancy, as haemorrhage into a lipomatous lesion can result in sudden increase in size and symptoms. Pleural lipomatosis, although exceedingly rare, should be maintained in the differential diagnosis for any well-defined, fat-attenuating pleural mass identified on conventional radiologic studies. Our patient opted for a conser-

vative approach and the lesion size remains stable at 2 years of initial diagnosis.

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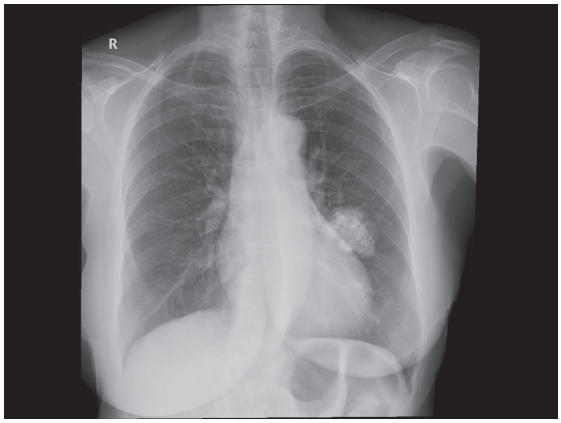

Figure 1

71 year old lady referred from neurology for evaluation of an incidentally detected chest X- ray lesion. She had no respiratory symptoms. Chest x-ray taken is given below (figure- 1). Her physical examination was normal.

Questions:

1. Identify the radiological sign
2. What is the probable diagnosis?

Answers

1. Popcorn calcification
2. Pulmonary hamartoma

She was further evaluated with PET CT to rule out any malignant transformation in the lesion. It revealed a FDG non avid left hilar lesion.

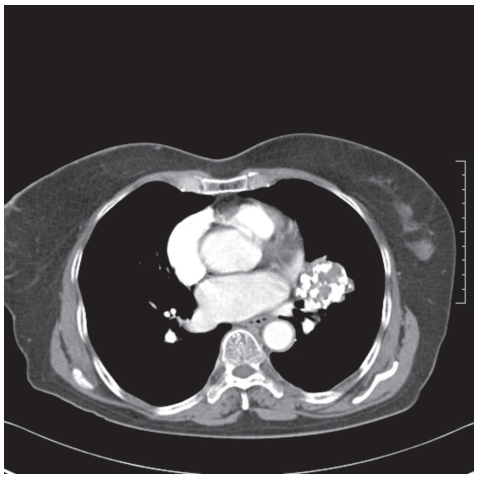

Figure 2 - Computed tomography chest

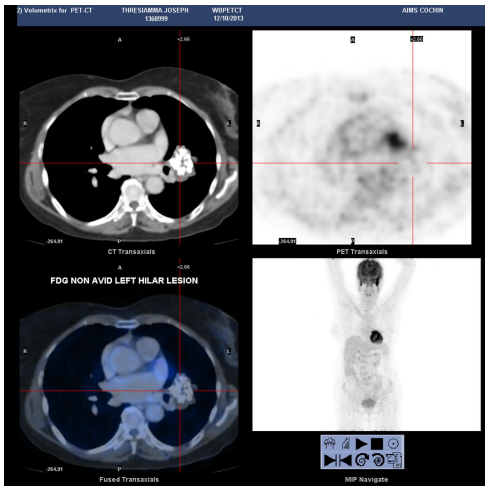

Figure-3- PET- CT image

She was advised to review after 6 months to look for any change in size of the lesion. But she was lost to follow up.

Discussion

Pulmonary hamartomas are the most common benign tumors of the lung. It can be seen in 0.25% of the population[1].These neoplasms are seen mainly peripherally but shows no lobar predilection. Hamartomas are 2–4 times more common in men compared to women. The disease usually occurs in the sixth and seventh decades of life.[2]

Majority of the pulmonary hamartomas are parenchymal. Hence most of these are asymptomatic and are incidentally detected in the chest radiograph. When endobronchial in location, hamartoma can present with hemoptysis or non resolving pneumonia. These patients can present with symptoms related to airway obstruction such as cough, hemoptysis, dyspnea, fever, etc.. There is a low risk for malignant transformation in hamartoma.[3]

Hamartomas are diagnosed by imaging. Parenchymal hamartomas are well circumscribed nodule or mass with smooth or slightly lobulated margins . Though popcorn calcification is the typical diagnostic feature, it may be seen only in 5–50% of the cases[4,5] Computed to-

1-Clinical Assistant professor
2-Clinical Professor
Department of Respiratory Medicine, Amrita Institute of Medical Sciences , Kochi

mography is superior to plain radiography in detecting intralesional fat and calcification. Fat may be identified in up to 60% of hamartomas in CT. The fat components may be localized or generalized within the nodule. Presence of fat in a well-circumscribed solitary pulmonary nodule which does not demonstrate significant growth is essentially pathognomonic of a pulmonary hamartoma and no further investigations are required[6]. If neither fat nor calcification is present, the differential is that of a solitary pulmonary nodule and is significantly broader.These cases would require a histological confirmation with Fine needle aspiration cytology/ surgical excision.

Most pulmonary hamartomas show a slow growth. So small lesions with no atypical features can be left alone with follow- up to exclude growth. But atypical lesions or endobronchial lesion causing symptoms needs surgical /endobronchial resection.

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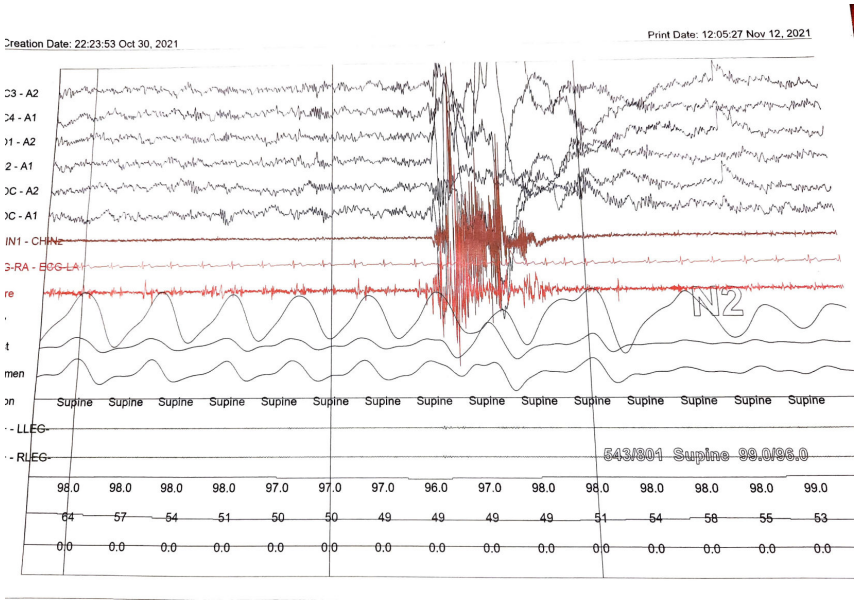

1. Identify the abnormality seen in the epoch shown above
2. What is the ASSM criteria for diagnosis of this condition?
3. Who are at high risk of developing this condition?

Answers

1. Bruxism
2. Criteria:
    a. At least twice the amplitude of baseline chin EMG activity
    b. At least 3 elevations of 0.25-2 seconds of increased chin EMG activity
    c. One elevation of greater than 2 seconds of increased chin EMG activity
3. Patients having the following condition are at greater risk:
    a. OSA
    b. Heavy snoring
    c. Alcohol use
    d. Smoking
    e. Caffeine intake
    f. Anxiety
    g. Highly stressful lifestyle

Discussion

Bruxism consists of an involuntary, aimless, repetitive, stereotyped oral activity characterized by teeth clenching or grinding. It is of two types - wakeful as well as sleep bruxism. Wakeful bruxism is found to occur in a variety of psychological, neurological, and orodental conditions. Sleep bruxism can occur during all stages of sleep, more often seen in N1 and N2 stages. Itis important to recognize and monitor bruxism as it can have long-term effects on the teeth, jawbones as well as the muscles of mastication. Bruxism exerts extremely powerful forces on the teeth, periodontal structures, temporomandibular joint, and masticatory muscles, and it often results in tooth wear and destruction, temporomandibular joint and muscle pain, as well as tension-type headache.[1]As in other disorders of sleep, the patient is blissfully unaware of the jaw activity, but the grinding noise can disrupt the sleep of the bedroom partner. The risk factors for the development of bruxism are OSA, heavy snoring, alcohol intake, smoking, caffeine intake, anxiety, and a highly stressful lifestyle.[2]The management of this condition includes the following - elimination of the suspected underlying cause and of various lifestyle factors known to enhance brux-

Senior Consultant and Group Coordinator,
Department of Respiratory Medicine,
Kerala Institute of Medical Sciences, Anayara P.O,
Trivandrum
dr.p.arjun@gmail.com

ism, periodic evaluation of the orodental condition, and use of occlusal splints (nightguards).[3]There is no evidence-based pharmacotherapy as of today. Intramuscular botulinum toxin injection is an increasingly popular option for severe bruxism, but its efficacy has not been evaluated in controlled clinical trials

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A case of Ewing Sarcoma of the rib with metastasis to chest wall

Deepak Paradkat[1], Kesavan Nair[2], C.M.Anusha[3]

Abstract

A 13-year-old girl presented to the Respiratory Medicine Department with complaints of left sided chest pain, progressive dyspnoea & fever of 1 month's duration. Clinical examination revealed diffuse swelling on antero-lateral aspect of left chest with moderate pleural effusion on the left side. FNAC from the swelling was suggestive of Askin tumor & pleural fluid was hemorrhagic with repeat cytology positive for malignant cells. Histopathology showed neoplastic cells with scanty cytoplasm, hyperchromatic nuclei and rosette formation suggestive of Ewing sarcoma, and on follow-up she developed metastasis in the upper part of chest wall. Because of this rare presentation we are reporting this case.

Keywords: Ewing's sarcoma; Pleural effusion; Rib.

Introduction

Ewing's sarcoma (ES) accounts for approximately 1% of all childhood cancers, it primarily involves soft tissue& bones. It is the second most common malignant bone tumor in the paediatric population.[1] Mean age group is 13 with male female ratio of approximately 1:2.ES family comprises of peripheral primitive neuroectodermal tumor (PNET) and Askin tumor.[2] Primary bone lesion involvespelvic bones, femur, fibula, clavicle, humerus and tibia. Other bones like rib & scapula are the infrequently involved.[3] As this was a rare presentation of the malignancy with metastasis after 2 years post surgery and chemotherapy, it encouraged us to report this case.

Case report

13-year-old girl presented at OPD with complaints of left sided chest pain, pricking type, more on coughing & deep breathing radiating to left axilla & shoulder. She also has breathing difficulty (NYHA 1à2) &low-grade fever over the period of 1 month.On general examination she was not dyspneic. Respiratory system examination showed sign of left sided moderate pleural effusion. Chest x ray showed left sided moderate pleural effusion. Aspirated approximately 400 ml of hemorrhagic pleural fluid, revealed a lymphocytic exudative pleural effusion (total cell count: 34 /dl, with lymphocytes [70%], proteins: 3.7g/dl; glucose: 25mg/dl, LDH: 33 IU/L). The total serum proteins and albumin were 5.7 and 4.2 g/dl respectively. pleural fluid wasnegative for malignant cells. CT chest revealed well lobulated heterogeneously enhancing lesion from the body of left 8th rib of approx 16.2 x 10.5×7.6 cm with moderate pleural effusion.

Thoracic surgeon was consulted. An excision biopsy from the site was done, which showed fragments from a highly cellular neoplasm with cells, arranged in irregular sheets and in groups with several endothelial lined spaces in between. Cells were small, round or oval with scanty cytoplasm and hyperchromatic nuclei. In some areas rosette formation were seen. IHC revealed Vimentin: Tumour cells- negative.CD99: Staining showed equivocal staining pattern. No definite cytoplasmic or membrane staining seen.

Patient was referred to oncologist and was started on chemotherapy. She was relatively better for approximately 2 years. Again, in December 2013 she reported with breathing difficulty.Radiological evaluation revealed 'Enhancing pleural based extra parenchymal nodular lesion seen involving posterior aspect of left upper thorax, largest measuring 4.8 X 3.8 cm and another along adjacent posterior mediastinal pleura 1.3 X 1.3 cm' for which she

1. Resident, KIMS , Trivandrum
2. Professor Department of Pulmonary Medicine, Shree UthradomThirunal Academy of Medical Sciences, Thiruvananthapuram
3. Senior Resident , Department of Pulmonary Medicine, Shree UthradomThirunaal Academy of Medical Sciences, Thiruvananthapuram

Corresponding author : Dr Kesavan Nair
Professor Department of Pulmonary Medicine,
Shree UthradomThirunal Academy of Medical Sciences, Thiruvananthapuram
Email : veekeyen@gmail.com

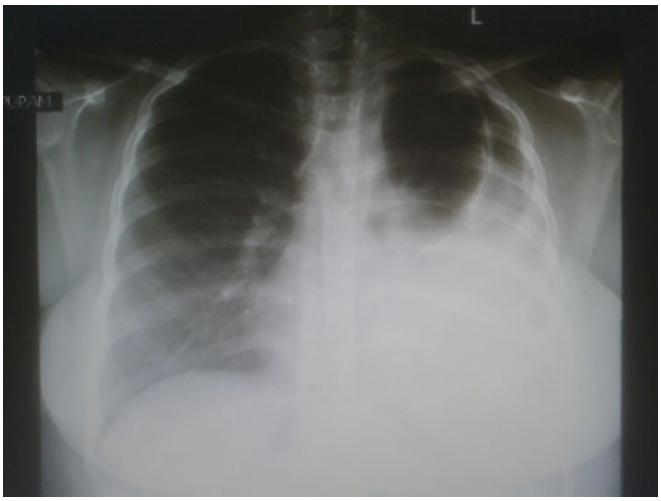

Fig 1: Chest X Ray PA view at the time of presentation

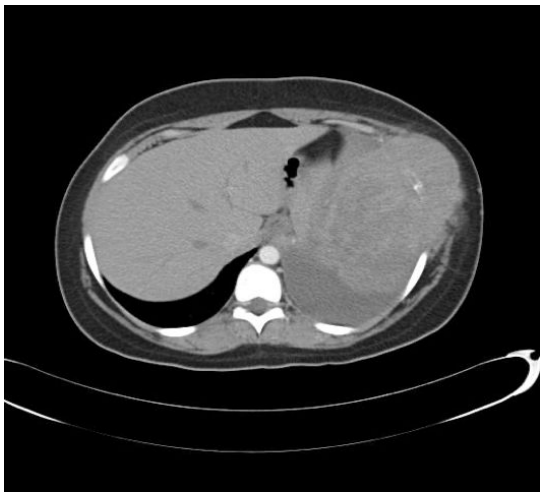

Fig 2 : mediastinal window showing the mass lesion

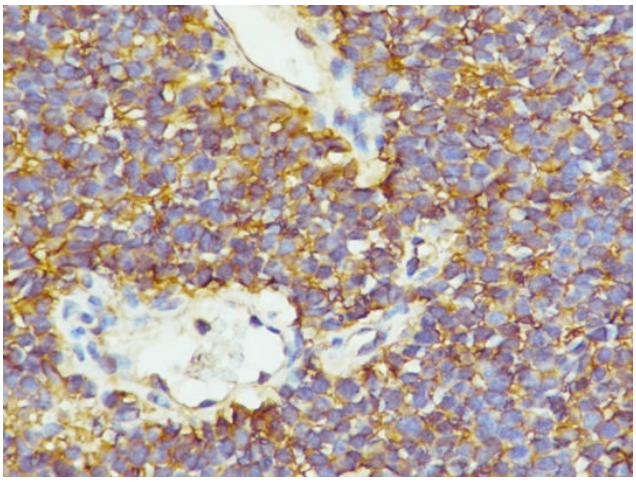

Fig 3: CD 99 positive of round cell tumor

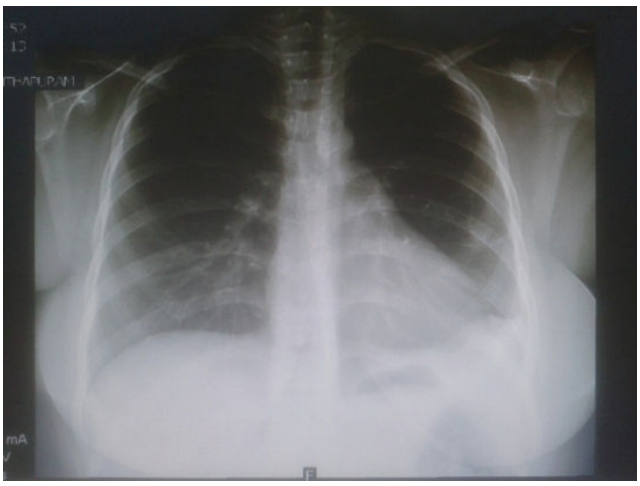

Fig 4: Chest X Ray Post Operative period (1 Month later)

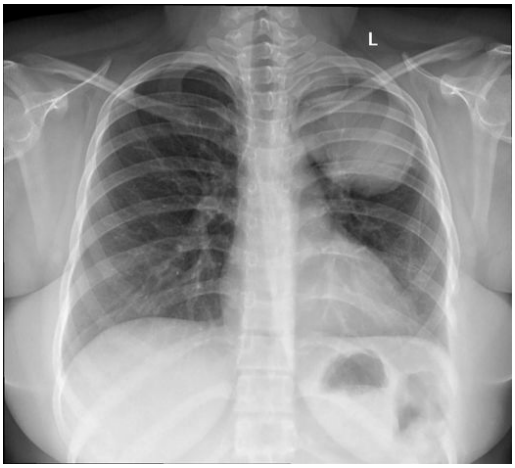

Fig 5: After 2 years of post operative period, showing left upper zone well demarcated lesion suggestive of encysted pleural effusion? Mass.

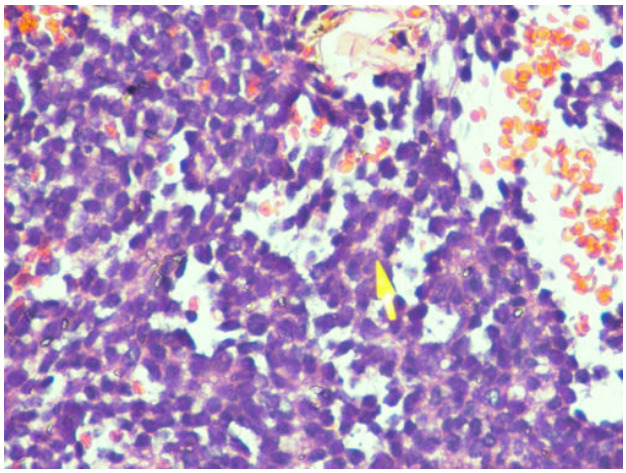

Fig 6: H & E staining of the biopsy tissue excised during second surgery which shows similar picture of round cell tumor

underwent excision of the mass. Histopathology revealed similar picture as previous.

Postoperative period, patient is doing well.

Discussion

Even though ES(historically known as Askin tumor) is not so uncommon now a days, ES of Rib is uncommon and most commonly affects children and teenagers. (11; 22) (q24; q12) a characteristic chromosomal translocation, is seen up to90% of cases.[4] These are small round cell sarcomas mainly arising from ribs but paravertebral, sternal and scapular localisations are reported.[8]In 1979, Askin et.al were the first ones to describe them in children, adolescent and young adults with female preponderance as in our case[9,10]. Eventually Askin tumor did not represent as a separate entity. In contrast molecular studies showed identical molecular findings as seen in Ewing's Sarcoma. Hence the terminology Askin tumor/ Primary neuroectodermal tumoris not recommended by WHO classification of bone and soft tissue tumor.

Systemic symptoms commonly encountered are fever, chest pain, malaise and sometimes respiratory distress due to intrathoracic mass.[11]Pleural effusion is an unusual finding[5]. Rarely patients initially present with pathological fracture or metastasis related symtoms.[12] ES of the ribs spread inwards towards the thoracic cavity and presents as extra pleural mass. In this case, pleural effusion was secondary to diffuse pleural involvement as proved by percutaneous chest wall biopsy along with thoracotomic rib and pleural biopsy. Rib cage is variably involved as seen radiologically. Affected rib shows predominantly lytic, mixed lytic sclerotic and sclerotic patterns.[6] In this case it was lytic lesion of the rib. Differential diagnosis includes group of undifferentiated small round cell sarcomas of bone and soft tissue, neuroblastoma, lymphoma, small cell carcinoma, rhabdomyosarcoma, monophasic synovial sarcoma and desmoplastic round cell tumor.[8]

Ultrasound can add as advantage in the absence of ionising radiation. It is easily accessible which gives real time images performed on patient bedside for aspiration of fluid. But confirmed diagnosis is made by biopsy& histopathological examination. The US showing chest wall masses usually appear as hyper echoic but can have anechoic if they have necrotic tissue or haemorrhagic fluid. Associated pleural effusion can be noted as seen in our case.[13]Doppler shows associated vascular flow.[14]

CT chest revealed well lobulated heterogeneously enhancing lesion from the body of left 8th rib of approximately 16.2 x 10.5×7.6 cm associated with moderate pleural effusion. Low attenuation may be present suggestive of necrosis or hemorrhage.Associated rib destruction is seen in 25-63% of cases.[14]

MRI though nonspecific can add advantage in better delineation of margins of the mass and the soft tissue involvement and also tumor staging.[14.15]Areas of necrosis and hemorrhage may be seen as high signal intensity on T1WI or T2WI compared to skeletal muscles. Gadolinium contrast enhances the solid component which represents hypervascularity.[14,16]

Fluoro deoxy positron emission tomography (FDG-PET) shows radio nuclear uptake and may be used in detection of primary lesion, residual or recurrent tumor or metastatic lesions.[14,15]

Histologically they are small round blue cell tumors- malignant group of neoplasms with wide differentials.[17]Diagnosis is based on combination of both clinical and imaging features as well as immunohistochemical staining and cytogenetic analysis.[18]Definitive diagnosis is made using Fluorescent in-situ hybridization (FISH) to detect the rearrangement of 22q12 (EWSR1) gene.[17]

Five year survival rates are approximately 50% once optimal treatment is achieved with multi-drug chemotherapy and subsequent resection of the rib and/or radiotherapy.[19] Due to the development of newer chemotherapeutic regimens in recent decades, there has been a remarkable improvement in survival rates.[7] The uniqueness of this case was that first it presented as a case of pleural effusion and second is that it recurred after optimal surgical and chemotherapy.

Conclusion

In summary, even though ES is not so uncommon now-a-days, primary rib involvementstill is uncommon. A high index of suspicion is required to make an accurate diagnosis which is confirmed by radiologic, histopathologic which is further confirmed by IHC examination. Timely multi disciplinary management involvement of Pulmonologist, Thoracic Surgeon, Pathologist & Oncologist plays the key role in prognosis of the disease

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A rare complication of left pneumonectomy

Venugopal Panicker[1], Shahina S[2], Preethi Augustine[2], Arjun Suresh[3], Shajahan PS[4], Bindu CG[5]

Abstract

Postpneumonectomy syndrome (PPS) is a rare complication of pneumonectomy occurring due to extreme rotation and malposition of mediastinum resulting in dynamic central airway compression between adjacent vascular structures and vertebra. Intrathoracic prosthesis placement is an evolving technique to treat this by alleviating the effects of thoracic dead space. We hereby present a case of post pneumonectomy syndrome which is rare in adults and further rarer following left pneumonectomy as in this case.

Key words: Postpneumonectomy syndrome, mediastinal prosthesis

Case report

A 56-year-oldgentleman, a never smoker, presented with progressively worsening of exertional dyspnea for the last 6 months. The breathlessness had progressed to Grade IV mMRC within a period of 6 months. Patient felt relieved on lying down in the prone position.

He did not have cough, expectoration, hemoptysis or palpitation. He had undergone left pneumonectomy 9 years ago for extensive bronchiectasis and was relatively symptom free till 6 months back. His routine blood investigations were within normal limits. His pulmonary functions were within expectation for left pneumonectomy and 6-minute walk test showed no desaturation but decreased 6MW distance to less than 100m.Echocardiography revealed mild pulmonary hypertension, which could not explain severity of his symptoms.

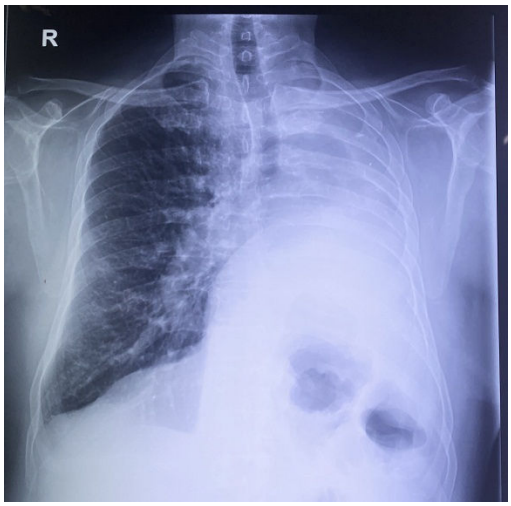

Fig 1 – Xray chest PA view

X-ray chest (Fig 1) shows homogenous opacification of left hemithorax with gross volume loss as indicated by shift of trachea, heart and left hemidiaphragm, which is consistent with left pneumonectomy.

CT- Thorax (Fig 2 & 3) revealed gross mediastinal shift to the left side and anterior herniation of the right upper lobe to the left hemithorax. The right main bronchus appears to be compressed between the right pulmonary artery and the vertebra. There was evidence of pulmonary hypertension too

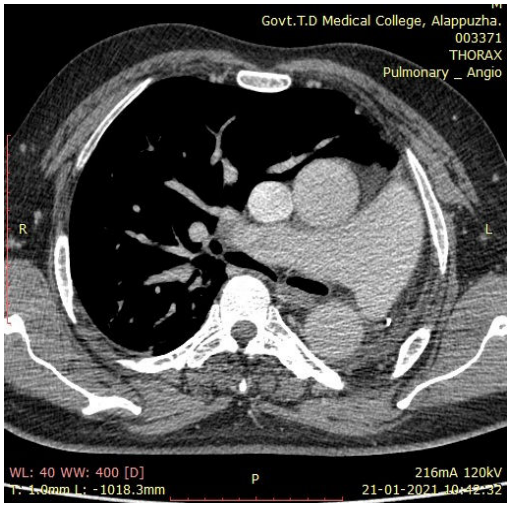

Fig 2 – CT thorax – mediastinal window

1. Professor & HOD, 2. Junior Resident, 3. Senior Resident, 4. Professor, 5. Associate Professor, Pulmonary Medicine, Government TD Medical College, Alappuzha.
Address for correspondence:
Venugopal P, Professor & HOD, Pulmonary Medicine, Government TD Medical College, Alappuzha. venuparijatham@gmail.com

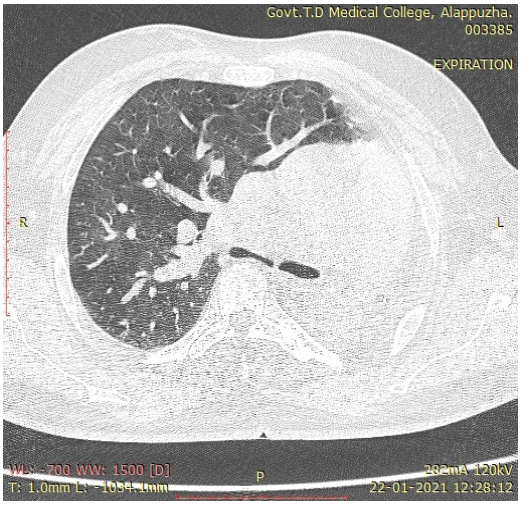

Fig 3- CT thorax lung window

A diagnosis of post pneumonectomy syndrome was made on the basis of radiological features, severe symptoms on exertion and partial relief on prone positioning. The patient was referred to thoracic surgery department, but the patient-was not willing for any further surgical intervention. He was not willing to undergo bronchoscopy too.

Discussion

The term postpneumonectomy syndrome (PPS) was first introduced by Wassermann et al. in 1979. Post pneumonectomy syndrome is a rare and delayed complication seen in only around 0.16% to 2% of cases after pneumonectomy. It comprises of excessive rotation and mediastinal shift resulting in compression of central airways and esophagus. It is not fully understood why PPS occurs only in a small subset of patients after pneumonectomy

After pneumonectomy, mediastinum shifts to the side of the removed lung. This results in rotation of the heart with compression of tracheobronchial tree (counterclockwise after right pneumonectomy or clockwise after left pneumonectomy). Herniation of remaining lung with over distension also occurs after the mediastinal shift. PPS is more commonly seen after a right pneumonectomy where the left main bronchus may be stretched over the descending aorta leading to its compression between aortic arch and pulmonary artery. After left pneumonectomy, the elongated right main bronchus can be compressed between the pulmonary artery and the thoracic spine, although this has been reported very rarely. However if there is a right aortic arch the right main or intermediate bronchus is compressed between the pulmonary artery and the right descending aorta leading to PPS after a left pneumonectomy. Sometimes tracheobronchomalacia may occur due to prolonged pressure in affected bronchus, which if present indicates poor prognosis. Similar complications may occur even after lobectomy (post lobectomy syndrome - PLS) although in that case anatomical and functional changes are less prominent[2].

There is usually a significant time gap between pneumonectomy and onset of symptoms. Post pneumonectomy syndrome is more common among children who also have a more acute course, attributed to increased mediastinal elasticity and lung compliance.

Clinical Presentation

Patient with PPS present with gradually progressive shortness of breath on exertion, wheezing, recurrent respiratory infection and a biphasic stridor. Many of these patients have recurrent episodes of pneumonia. Compression of esophagus may lead to symptoms of dysphagia and heartburn[1]. Dysphagia is more common after right pneumonectomy. Recurrent laryngeal nerve palsy has also been described in several patients due to prolonged traction on the nerve caused by the mediastinal shift. Some patients with extreme mediastinal shift may be still remain asymptomatic.

Dyspnoea is not an uncommon symptom in postpneumonectomy patients and it can be due to worse preoperative baseline lung function or recurrence of conditions leading to pneumonectomy. Clinical examination may often lead to a wrong diagnosis of a cardiovascular problem as the cause of dypnoea in PPS. Therefore diagnosis of PPS as the cause of dyspnoea must be made by exclusion.

Diagnosis

Diagnosis is usually radiological. Chest X-ray shows opacification of involved hemithorax with grossly hyperinflated remaining lung and shift of mediastinal structures towards the removed lung side. CT scan is the modality of choice for diagnosis. It shows abnormal stretching and kinking of the distal part of the trachea and the main bronchus entrapped between the pulmonary artery anteriorly and the aorta and spine posteriorly. In addition, esophageal deviation, counter clock rotation of heart along with compression of right ventricle may also be seen.

In some patients, airway compression occurs only during exertion, which can be appreciated only by dynamic slice CT or a dynamic bronchoscopy. Routine CT scan may not show narrowed bronchus in such cases.

Pulmonary function tests (PFT) - forced vital capacity (FVC) may be higher than expected in patients after pneumonectomy because of overexpansion of the remaining lung. It has also been observed that in patients with PPS there is marked rise in flow rates and FVC in the sitting as compared to the supine position.

Treatment[3]

Main aim of treatment is to reposition the mediastinal structures to the midline. Reposition of the mediastinum, adhesiolysis and fixation by implantation of a thoracic prosthesis is the treatment of choice. Both silicone prosthesis and saline filled prosthesis are used for this purpose. Intraoperative bronchoscopy is recommended to look for improvement in airway patency before chest closure. Other surgical procedures such as pericardial fixation including complex reconstruction are also done. In high risk patients tracheobronchial stenting can be done but stent migration and fistulation with the pulmonary artery or descending aorta have been reported. Surgical repositioning often provides immediate and lasting relief to the patient. For those patients who are unfit or unwilling for surgery, endobronchial silicone or hybrid stent placement is an alternative approach[5]. Non invasive ventilation could serve as a "pneumatic stent" keeping the airways patent until placing an endobronchial stent or during the preoperative preparation of the patient.

Challenges faced by anesthesiologists during anaesthesia have been reported. They include difficult intubation caused by grossly distorted mediastinum, difficulty in ventilation, and hemodynamic instability. The dynamic airway compression may lead to complete collapse of the airways after induction of anesthesia and muscle relaxation. It may be necessary to bypass the narrowed segment of bronchi in order to adequately ventilate the patient. Patients with severe bronchial obstruction may need micro laryngeal ETT and airway exchange catheter with the ability to ventilate, bronchial dilation, and in cases of severe airway narrowing, veno-venous or venoarterial extracorporeal membrane oxygenation (ECMO)[6].

Post pneumonectomy like syndrome[7]

This condition is recurrent laryngeal nerve palsy, dysphagia and dyspnea in patients with agenesis of left lung or destroyed lung. It is treated by division of ligamentum arteriosum, fixation of aorta, or pulmonary artery to sternum, placement of expandable stents, etc. Mediastinal repositioning by adhesiolysis and prosthesis to fill the free space is also effective.

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