Pulmon

The Journal of Respiratory Sciences

Vol 21, Number 3, (Sep - Dec) 2019

ISSN 0973-3809

OFFICIAL PUBLICATION OF ACADEMY OF PULMONARY AND CRITICAL CARE MEDICINE

Contents

Vol 21, Number 3, (Sep – Dec) 2019 ISSN 0973 - 3809

Pulmon

The Journal of Respiratory Sciences

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Pulmon

The Journal of Respiratory Sciences

Pulmon 2019 ; 21:3 109-180

Proprietor
Academy of Pulmonary and Critical Care Medicine
Head office - Ernakulam

Publication data
3 issue published in a year

Web site: www.apccm.in

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Subscription rates
Personal
Single :Rs 250
Annual:Rs. 600
Institutional
Single : Rs. 250
Annual : Rs. 600
E-mail ID: editorpulmon2019@gmail.com

Intructions for Authors

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

Registration

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

Type setting and Printing

Asoka Press, Gandhinagar
Kottayam
Ph: 9249821014

Pulmon The Journal of Respiratory Sciences

"Committed to the care of the Lungs"
The Official Publication of the
Academy of Pulmonary and Critical Care Medicine

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Academy of Pulmonary & Critical Care Medicine

Pulmon

The Journal of Respiratory Sciences

Editorial

Biomarkers in COPD

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Chronic obstructive lung disease is a chronic disease with relentless progression with major risk factors of smoking, having irreversible airflow obstruction with varying phenotypes characterised by productive cough with dyspnoea. It is a major cause of morbidity and mortality worldwide. The treatment remains mainly focused on reducing airflow obstruction and the number of exacerbations. The usual measures of clinical outcome are subjective with reduced dyspnoea and sputum production. For the evaluation of disease modifying drugs, it is necessary to have a biomarker which can indicate the presence of disease or for establishing a treatment end point and predicting outcomes. The search for a molecular signature predicting decline in lung function is interesting. Though there many biomarkers that have been studied, there is little information of a reproducible biomarker which can help in assessment of clinical outcomes in Chronic obstructive pulmonary disease

Biomarkers are like signatures of a disease process, acknowledging the presence of a disease. It should be easily accessible and be able to prognosticate and also reveal the extent of response to therapy.It is vital and essential component of precision medicine.

In a working group of the National Institutes of Health focussing on biomarkers and surrogate end points, a biomarker was defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention''[1]

Normally clinical endpoints are used to assess response to intervention, but the surrogate endpoint is used when a biomarker is used to mark a clinical end point.[2]

COPD being a chronic disease characterised by dyspnoea and productive cough, the first search for a biomarker would be characterising dyspnoea and parameters to quantify dyspnoea.

The major biomarker for COPD has been a low forced expiratory volume in 1s (FEV1) with lung function testing, but it cannot distinguish between the various phenotypes of COPD. Clinically diagnosed with a symptom of cough and sputum or dyspnoea, these remain too subjective to be used in the management of the disease. Although, FEV1 is easy to obtain and reproducible, it does not distinguish between phenotypes and is not specific for COPD and is unresponsive to some therapies that is known to improve survival like long term oxygen[3].

In most cases, biomarkers fail because of poor reproducibility and inability to transfer data from laboratory to clinical use. The study by Hollander, Zsuzsanna et al addresses the characteristics of good new biomarker as a biomarker likely to be superior[2], actionable[3], valuable[4], economical[5] and clinically deployable[4].

In order to address problems in the development and approval of biomarkers in COPD in 2010 the COPD foundation established the COPD Biomarkers Qualification consortium(CBQC)[5].

Various sputum biomarkers like sputum eosinophilia and sputum neutrophilia has been studied. There has been considerable interest in studying the use of established cardiac biomarkers and the correlation in COPD like serum cardiac troponin I and Brain natriuretic peptide.

Cardiovascular comorbidities exist in COPD.The study by Baillardetal showed that serum cardiac troponin I is an independent predictor of mortality in acute exacerbation of COPD[6].

Even in mild to moderate COPD succumb to cardiovascular disease[7].The exact mechanism which causes rise in these cardiac specific markers need to be studied and whether they are chronically elevated.

B-Type natriuretic peptide (BNP) is a hormone secreted by cardiomyocytes in the heart ventricles in response to cardiac stress and ventricular dysfunction.

After its synthesis the proBNP precursor is cleaved into the active BNP hormone and an inactive NT-proBNP fragment. The functions of BNP include vasodilatation, natriuresis and inhibition of rennin angiotensin aldosterone system[8].

The interest in plasma brain natriuretic peptide as biomarker has been there to assess chronic obstructive pulmonary diseases as it is an established biomarker for monitoring heart failure. It is well known fact that COPD is associated with cor pulmonale and pulmonary hypertension and is related to poor exercise capacity and plasma brain natriuretic peptide [BNP] is a useful biomarker for heart failure[8].

Plasma BNP has been studied in stable chronic obstructive pulmonary diseases. In a study by Yoko Kida et al, plasma BNP correlated with exercise capacity in stable chronic lung diseases[9].

The discovery and validation of biomarkers of myocardial injury and ventricular overload such as troponin and brain-natriuretic peptide (BNP) has transformed the diagnosis, management and design of clinical trials in conditions such as myocardial infarction and congestive heart failure[10].

However, it does not translate into usefulness in predicting a COPD exacerbation. Plasma Brain natriuretic factor would remain a useful tool to assess patient of chronic obstructive lung disease with associated cor pulmonale, though may not be effective for routine evaluation of exacerbations in COPD patients.

Plasma Prosurfactant Protein B is produced in the lung by type 2 alveolar pneumocytes and non-ciliated bronchiolar epithelial cells.It has anti-inflammatory and anti-oxidative properties making it useful for studying diseases like acute respiratory distress syndrome and neonatal respiratory distress syndrome[11] Its effectiveness as a biomarker for COPD is being evaluated.

Chronic obstructive lung disease is a disease with systemic inflammation as reflected by blood biomarkers such as interleukin[I6],Creactive protein (CRP), fibrinogen and leukocytes and is likely associated with many pulmonary and extra pulmonary manifestations[12,13,14]

At a threshold of 350 mg/dL, 9.5% (266/2807) of participants with low fibrinogen in the studies had a hospitalized exacerbation within 12 months, com-

pared to **16.8**% (401/2392) of patients with high fibrinogen. The percentage of participants with high fibrinogen who experienced a hospitalized exacerbation exceeded that of those with low fibrinogen in each study assessed. High fibrinogen was associated with an increased risk of hospitalized COPD exacerbations within 12 months[14]

An integrated analysis of participant-level data from 5 individual studies demonstrated that plasma fibrinogen ≥350 mg/dL was associated with an increased risk of subsequent hospitalized COPD exacerbations within 12 months and all-cause mortality within 36 months[14].

Although biomarkers do not need to have biological relevance, it is unlikely that fibrinogen will directly affect COPD mortality or the hospitalised COPD exacerbations.

Fibrinogen may thus be a promising biomarker for a generalised state of inflammation or a marker for poly morbidity that increases the chance that a small event will lead to a worse outcome[15].

Fibrinogen and other markers of systemic inflammation are elevated in the context of acute COPD exacerbations and may also identify those at risk of accelerated lung function decline and hospitalization[15].

There are other potential blood biomarkers include pulmonary and activation regulated chemokine (PARC/CCL-18) and a Clara cell secretory protein 16 (CC-16).[16]

Computed Tomography provides a means to assess phenotypes and identify the relative extents of small airway disease, which themselves may inform prognosis and therapeutic decision[16]

The lack of well validated markers for COPD marks the need of the hour to find the right biomarker. There may be difference in the aetiology and biomarkers between non-smokers and smokers or never smokers and ex-smokers with COPD. This has not been addressed adequately in various studies as most population studied are often smokers with COPD.

The duration of COPD is a long term with various twists and turns in terms of hospitalizations for infective exacerbations, usage of steroids or presence of lung malignancy which can alter the presence of biomarkers;however, most studies are short term.

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Review article

Mycoses: Diagnosis & Treatment

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There is an increase in the general prevalence of fungal infections, which could probably be a reflection of the increasing awareness and availability of superior fungal diagnostic methods. The increasing prevalence of fungal infections in the South Indian state of Kerala especially in the past 2 years however, can be extrapolated from the ideal fungal sporulating grounds yielded by the 2 consecutive years of floods. Whichever be the actual reason, the rising trend of fungal infections warrants a good understanding of fungal infections, the diagnostic modalities with their utility, and the treatment options.

Fungal infections can broadly be classified into superficial, cutaneous, sub-cutaneous, deep and invasive fungal infections[1]. Superficial fungal infections include Pityriasis versicolor,Piedrahortae and Exophiala wernickii. Cutaneous type includes the entire spectrum of Dermatophytic infections, and cutaneous Candidiasis. Actinomycosis, Sporotrichosis and Chromoblastomycosis constitute the subcutaneous mycosis. Deep/systemic mycosis include the fungal infections pertaining to and restricted to specific systems of the human body like meningitis & pneumonia. They may be primary or opportunistic. Primary agents include *Coccidoides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatidis* and *Paracoccidoides brasiliensis*[1]. Invasive fungal infection refers to multi-system involvement, and is often witnessed & documented in the immunosuppressed cadre of patients, than in the general population. (Figure 1)

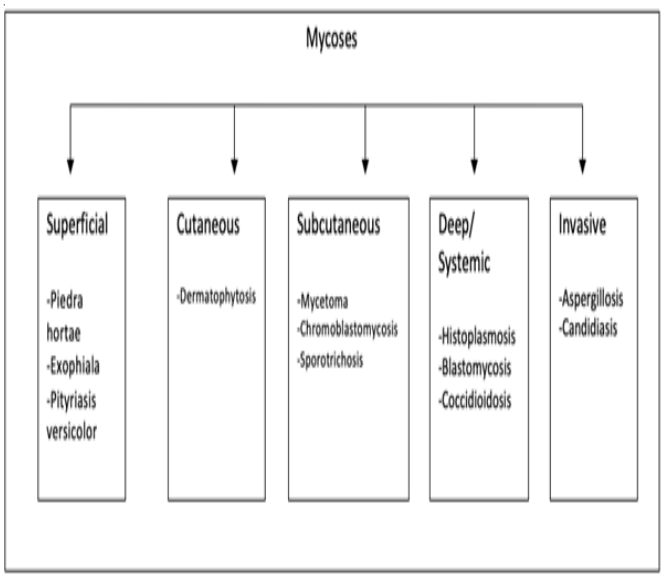

Figure 1: Classification of Mycoses based on extent of involvement[1]

In view of the ever-increasing list of fungal diagnostic methods, it is empirical that we understand the scope of each of these, which

will thereby enable us to make the right choice for a given scenario. The laboratory diagnostic methods range from the simple, yet effective direct microscopy, to the Nobel prize winning method of MALDI-TOF. (Figure 2)

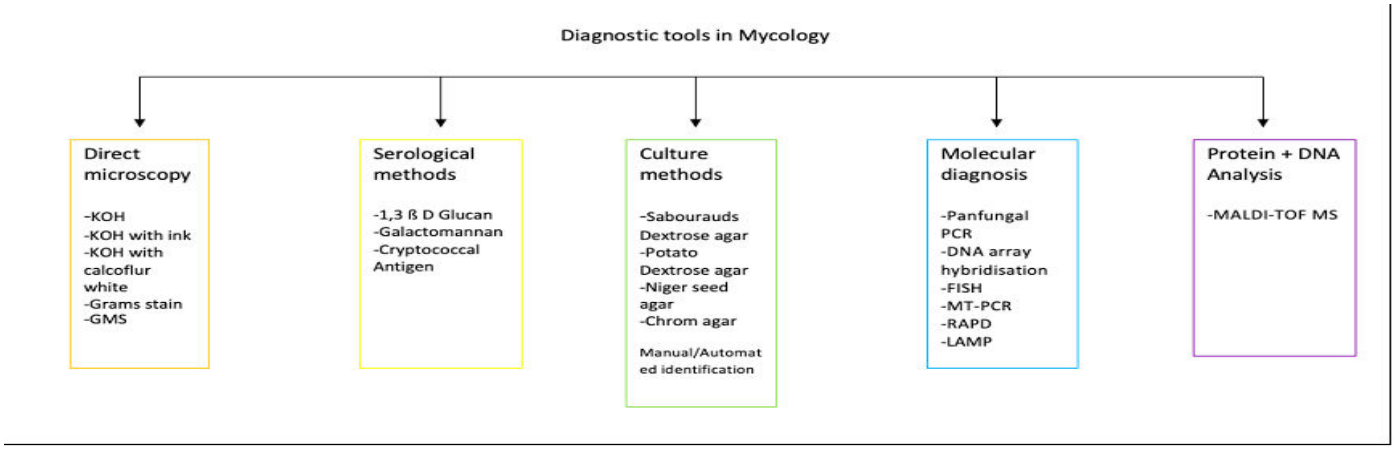

Figure 2: The diagnostic modalities available for determining the causative agents in Mycoses (KOH= Potassium hydroxide, GMS= Gomori's Methanamine Silver, PCR= Polymerase Chain Reaction, FISH= Flourescent InSItu Hybridisation, MT-PCR= Multiplex Tandem PCR), RAPD=Random Amplified Polymorphic DNA, LAMP= Loop Mediated Isothermal Amplification assay, MALDI-TOF MS= Matrix Assisted Laser Desorption Ionisation Time of Flight Mass Spectrometry)[3]

Direct microscopy can be of much use, provided the right method is chosen. It holds the added advantage of low Turn-around-Time, and seasoned eyes can pick-up and predict as much from direct microscopy as can be obtained from 3 weeks of fungal culture. The various options include direct microscopy by KOH mount (10%/40% depending on the amount & nature of organic debris in the clinical sample), fluorescent microscopy by KOH with Calcofluor white which is a highly sensitive method, and if not for the false positivity, is a method that can solely be resorted to[2]. The age old, time tested method of Gomori's Methanamine Silver (GMS) is probably the best and yields the least controversial results; but is at a disadvantage due to the labour intensive and exhaustive multi-step staining process.

It is of much importance in the diagnosis of *Pneumocystis jiroveci* pneumonia, and the positive predictive value from BAL samples is very high. India-ink staining, a simple step method can be invaluable in the diagnosis of Cryptococcal meningitis, as it has a high positive predictive value and low turn-around-time; it has probably lost significance in the light of newer serological methods which are less exhaustive and as specific.

Serological methods include various antigen detection methods. Antibody is hardly looked for, as their values were found to be confounding probably due to the continual exposure to fungal agents from the environment.T The assays which are increasingly being uti-

lized, especially by the intensivists and pulmonologists are 1,3, ß D glucan & Galactomannan assays. *Paecilomyces* species, *Penicillium* species, Aspergillus species and many other filamentous fungi have Galactomannan in their cell wall. Of these, *Aspergillus* has Galactomannan in higher amounts, and therefore, quantification of Galactomannan is considered specific for diagnosis of Aspergillosis. Especially in cases of invasive Aspergillosis, Galactomannan when combined with high-resolution CT helps in early diagnosis. Cryptococcal antigen test is very useful for diagnosis of Cryptococcal meningitis; the low turn-around-time of the test proving it to be an ideal screening method for the nature of urgency of the clinical context in which it is often requested.

Culture methods for diagnosis of fungal infections are wide and varied. From the choice of sample, to the culture medium chosen for the sample, every step depends on the clinical details including clinical presentation, the acute/ chronic nature of the symptom, co-morbidities, underlying diseases, medications and the system/s involved. A well performed culture of an aseptically collected sample can help in the diagnosis of even challenging cases like disseminated Histoplasmosis. It would serve well to discuss with a Clinical Microbiologist for choice of an ideal sample based on the clinical context. Most cultures are incubated at a minimum of 2 different temperatures (25°C and 37°C), as a good fraction of pathogenic fungi are thermally dimorphic. The choice of culture medium is often done based on the presentation & clinical diagnosis, along with valuable information from the direct microscopy of the sample. For fungal culture to be declared negative/ No growth, it requires 3 weeks/ 21 days of incubation. Growth obtained at any point within this time frame is processed to determine the Genus and species. Wherever possible, speciation maybe done via Vitek 2 automated system or utilising the identification flow charts. The antifungal susceptibility of yeasts and yeast like fungi can be obtained via automated systems in 2 days of getting a growth in culture; whereas antifungal susceptibility of mould-type fungus is to be determined by micro-broth dilution method, which is often time-consuming and therefore not resorted to unless clinically indicated[21].

Molecular methods yield conclusive results, provided, a good quality specimen is obtained, and an ideal investigation is chosen. Available options in molecular diagnosis include DNA array hybridisation, Fluorescent in situ Hybridisation, Multiplex tandem PCR (MT-PCR), Real time PCR, PCR-ELISA, Random Amplified Polymorphic DNA (RAPD) and

Loop mediated Isothermal Amplification (LAMP)[4].

Matrix Assisted Laser Desorption Ionisation- time of flight mass spectrometry, is protein & DNA analysis method that helps in rapid detection and accurately identifying the fungal species: yeast as well as filamentous fungi. This gains much importance in the identification of significant resistant isolates like *Candida Auris* which are often misidentified by manual as well as automated systems[5].

Antifungal Antibiotics

1) Griseofulvin
2) Allylamines
   - Terbenafine
3) Pyrimidine analogues
   - Flucytosine
4) Azoles
   - Imidazoles
     - Clotrimazole, Ketoconazole
   - Triazoles
     - Fluconazole, Itraconazole, Posaconazole, Voriconazole
5) Amphotericin B
   - Amphotericin B Deoxycholate
   - Lipid associated formulations
     - Amphotericin B Colloidal Dispersion(ABCD)
     - Amphotercin B Lipid Complex (ABLC)
     - Liposomal Amphotericin B
6) Echinocandins
   - Caspofungin, Micafungin, Anidulafungin
7) Topical antifungals
   - Clotrimazole, Econazole, Miconazole, Terconazole, Butoconazole, Oxiconazole
   - Ciclopirox Olamine
   - Haloprogin
   - Tolnaftate
   - Naftifine, Terbinafine, Butenafine
   - Benzoic acid, Salicylic acid, Undecylenic acid

Figure 3: Classification of antifungal antibiotics, based on mechanism of action.[6]

The correct identification of the fungal pathogen implicated, significantly uncomplicates the decision regarding choice of antifungal antibiotic. The main classes of antifungal antibiotics are imidazole, triazoles, pyrimidine analogues, polyenes, echinocandins and various newer classes of antifungals[6]. These antibiotic classes significantly differ in their mechanism of action. (Figure 3)

Griseofulvin

Griseofulvin is a microtubule assembly inhibitor achieving fungistatic effect[8]. is deposited in keratin precursor cells, and as these cells grow and differentiate, griseofulvin remains tightly bound to keratin, thereby endowing on these cells prolonged resistance to fungal invasion. Due to this, newly grown hair and nails are often the first to be free of the fungal manifestations. These characteristics make it a near-perfect choice for the treatment of Dermatophytoses, whenever susceptible.

Allylamine

Terbinafine is a synthetic allylamine. It acts by blocking ergosterol biosynthesis through inhibition of squalene epoxidase enzyme (Figure 4)[9]. It is well absorbed, but a bioavailability of only 40% because of first pass metabolism in liver. It accumulates in skin, nails and fat, making it a suitable choice for superficial fungal infections caused by sensitive strains. It is not recommended in patients with

marked azotemia or hepatic failure[6]. Terbinafine concentration decreases with rifampin and increases with cimetidine. Oral formulations of terbinafine has been found to be as effective as itraconazole for onychomycosis.

this assures its selective action[10]. It has useful activity against *Cryptococcus*, *Candida* and agents of chromoblastomycosis.

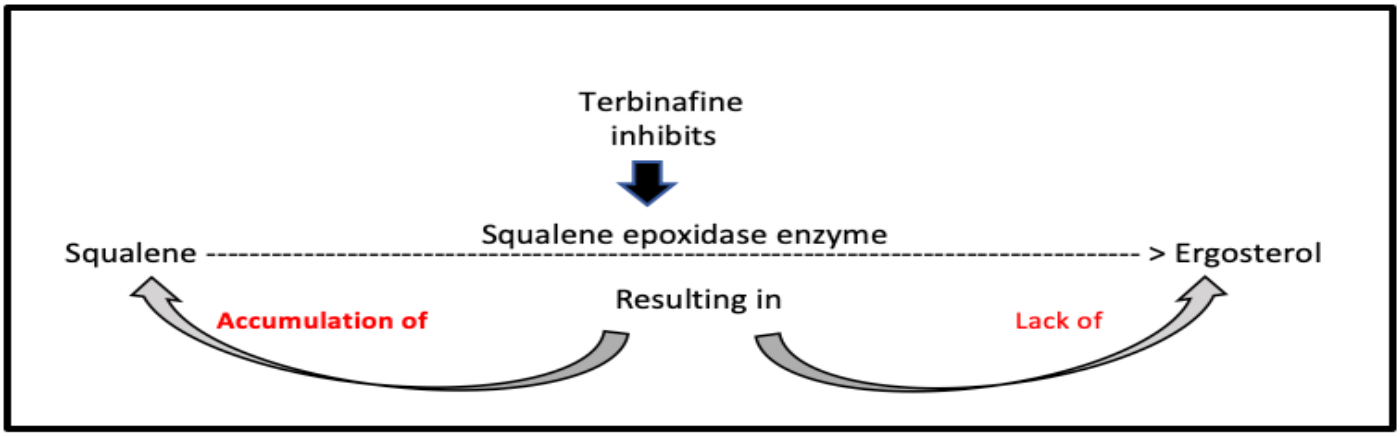

Figure 4: Mechanism of action of the allylamine Terbinafine. The lack of ergosterol results in altered cell permeability leading to cell death; and on the other hand, accumulation of squalene, the ergosterol precursor, leads to cell toxicity and thereby enhances cell death[9].

Pyrimidine Analogue

Flucytosine is a fluorinated pyrimidine. All susceptible fungi are capable of deaminating flucytosine to 5-fluorouracil. Mammalian cells have little or no cytosine deaminase, which prevents its metabolism to fluorouracil, and

Secondary resistance (resistance arising during therapy) is a common reason for therapeutic failure, when this agent is used alone. It is therefore often used in combination of Amphotericin B (Figure 5).

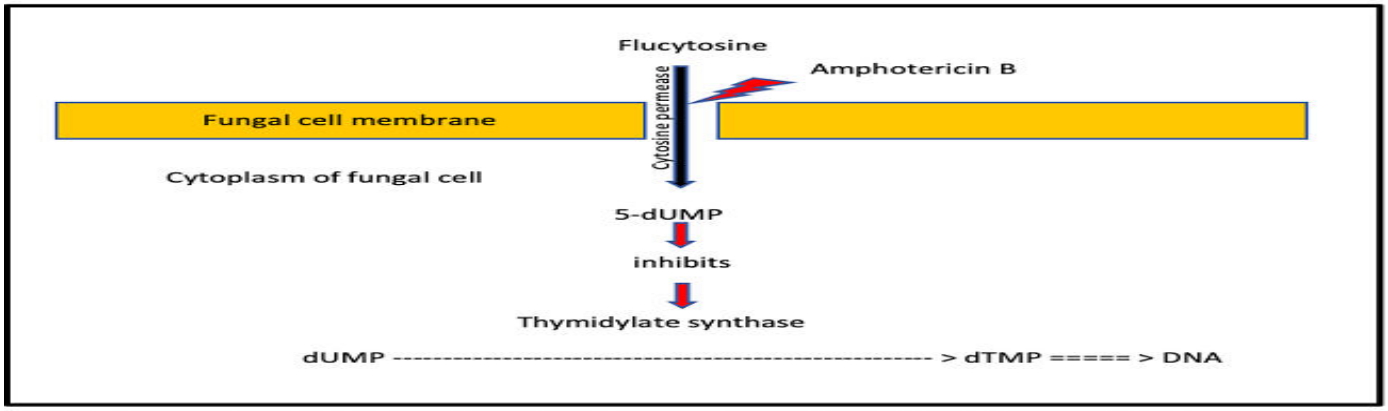

Figure 5: Susceptible fungi convert Flucytosine to 5-dUMP which is a potent inhibitor of thymidylate synthase, and its finally results in inhibition of fungal DNA synthesis. Simultaneous administration of Amphotericin B produces pores on the cell membrane which facilitate entry on Flucytosine into the cell and thereby increase the intracellular concentration of Flucytosine[10].

Azoles

Azole antifungals include 2 broad classes, imidazole's and triazoles which have the same mechanism of action and are similar in their spectrum of activity. Triazoles were formed as a result of N-substitution of imidazole, due to which they have slightly broader spectrum of activity and less effect on human sterol synthesis. Azoles as a group have clinically useful activity against *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*,*Coccidioides* species, *Paracoccidioides brasiliensis*, and ringworm (dermatophytes). *Aspergillus* spp, *Scedosporium apiospermum* (*Pseudallescheriaboydii*), *Fusarium*, and *Sporothrix schenckii* are intermediate in susceptibility. *Candida krusei* and the agents of mucormycosis are resistant. Azoles inhibit the biosynthesis of ergosterol, which is required for the formation of cytoplasmic membrane and lead to the accumulation of 14-alpha-methyl-sterols[11]. The accumulation of these methyl sterols impairs the function of certain membrane-bound enzyme systems such as ATPase and the enzymes of the electron transport system and thereby inhibit fungal growth (Figure 6).

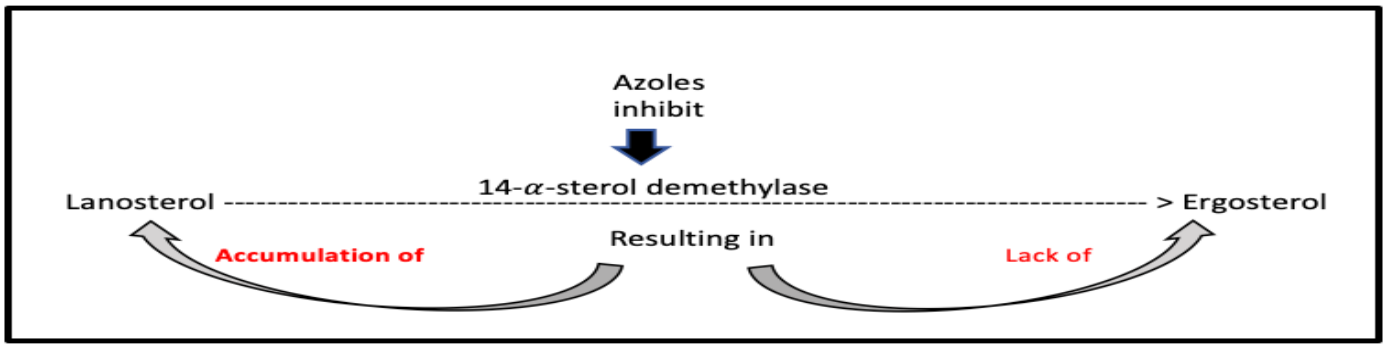

Figure 6: Mechanism of action of the Azoles (Imidazoles as well as triazoles). The lack of ergosterol results in altered cell permeability leading to cell death; and on the other hand, accumulation of 14- α -methyl sterols impairs the functioning of certain membrane bound systems such as ATPase and enxymes of the electron transport system, and thus inhibits the growth of the fungi[6].

the imidazole, are metabolized more slowly and have less effect on human sterol synthesis[12]. Azoles continue to be high up in the market, probably due to their broad spectrum of activity, oral bioavailability and the remarkably low toxicity. Azole resistance has emerged gradually during prolonged azole therapy. Resistance mechanisms mainly consist of increased drug efflux and altered or increased C14 alpha demethylase.

Itraconazole: Oral absorption of the capsule is significantly enhanced by food, although absorption of the solution is best on an empty stomach. Tissue, pus and bronchial secretion

concentrations are generally higher than plasma concentrations[13]. It is useful in the treatment of invasive Aspergillosis, allergic bronchopulmonary aspergillosis, blastomycosis, histoplasmosis, meningeal and non-meningeal coccidioidomycosis and phaeohyphomycosis. Although not an approved use, itraconazole is a reasonable choice for the treatment of pseudallescheriasis[14], an infection not responding to amphotericin B therapy, as well as cutaneous and extracutaneoussporotrichosis. Its use as prophylactic agent in AIDS patients to prevent relapse of Histoplasmosis is associated with high success rates. Itraconazole has many clinically relevant drug interactions (Figure 7)[11].

Fluconazole: Fluconazole has good oral bioavailability with more than 80% of the drug found in circulation. Concentrations of fluconazole in CSF are close to 70% of the blood levels, irrespective of meningeal inflammation[15]. Excellent penetration is documented into saliva, urine and other body fluids. The excellent drug penetration into all body compartments moots the need for local instillation into CSF, bladder or any other site. Oral formulations are found to have excellent efficacy in oropharyngeal and esophageal candidiasis and topical formulation for vulvovaginal candidiasis. It is advised in Candida septicemia, cryptococcal meningitis and as prophylaxis in preterm neonates. However, a direct comparison of fluconazole with itraconazole showed the latter to be superior for skeletal infections[16]. Based on evidence of teratogenicity in animals, Fluconazole has been placed in pregnancy category D, meaning it should be avoided in pregnancy.

Posaconazole: Posaconazole is lipophilic and has a volume of distribution greater than body water, suggesting extensive distribution and tissue penetration. Its main indications include moderate-to severe graft-versus-host disease and as prophylaxis of invasive fungal infections in neutropenic. It is found to be much more effective than other azole antifungals in preventing breakthrough fungal infections and as prophylaxis during cancer chemotherapy[17]. It is of much use in the prevention of invasive fungal infections in general, and aspergillosis in particular. However, limited available data points towards poor CNS perfusion of the drug, thereby limiting its use in infections of that site[18].

Voriconazole: Voriconazole has a structure similar to Fluconazole, but has documented increase in vitro activity. With 96% oral bioavailability, its use is often complicated due to the non-linear metabolism[19]. At higher doses, there occurs a greater than the extrapolated linear increase in drug exposure.

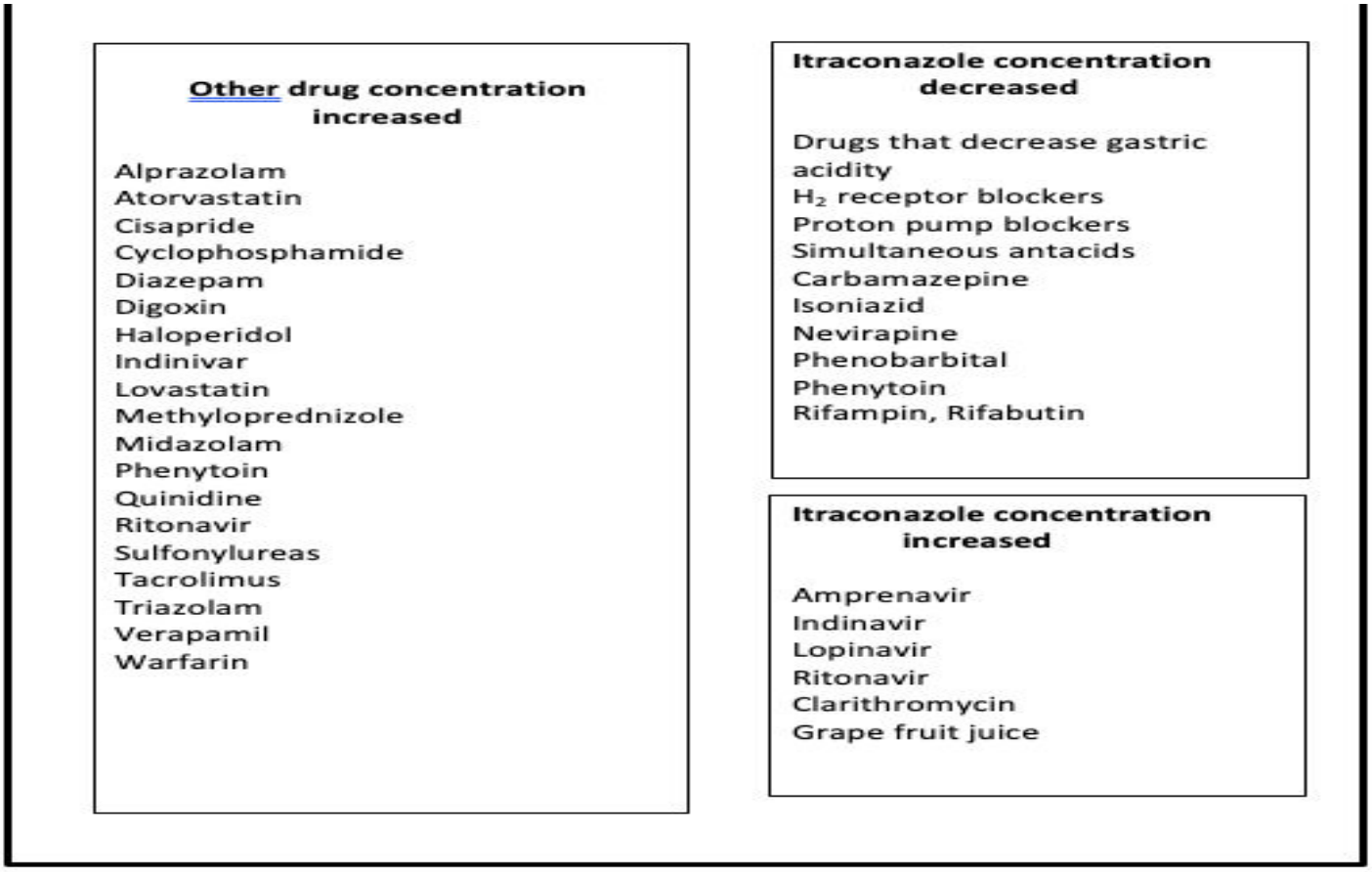

Fig. 7 interactions of Itraconazole with other drugs.[6,11]

It was found to be superior to C-AMB in invasive aspergillosis; with better documented survival rate as well. Co-administration with rifampin, rifabutin or ritonavir is contraindicated because of accelerated voriconazole metabolism. Co-administration with NNRTIs (Non-nucleoside reverse transcriptase inhibitors) results in increase of voriconazole metabolism and decrease in NNRTI metabolism. When given with phenytoin, voriconazole dose should be doubled. Voriconazole was found to be teratogenic in animals and therefore is contraindicated in pregnancy (Class D).

Triazoles in the pipeline: Isavuconazole, albaconazole and ravuconazole are triazoles. All three appear to have good antifungal spectra.

Amphotericin B

Amphotericin B is a heptaene macrolide. It derives its name from amphoteric nature. Its use is complicated by poor aqueous solubility and further by the substantial toxicity on parenteral administration. It acts by binding to the ergosterol that is present in the membrane of sensitive fungi, resulting in the formation of pores or channels that increase the permeability of the membrane, eventually leading to cell death (Figure 8).

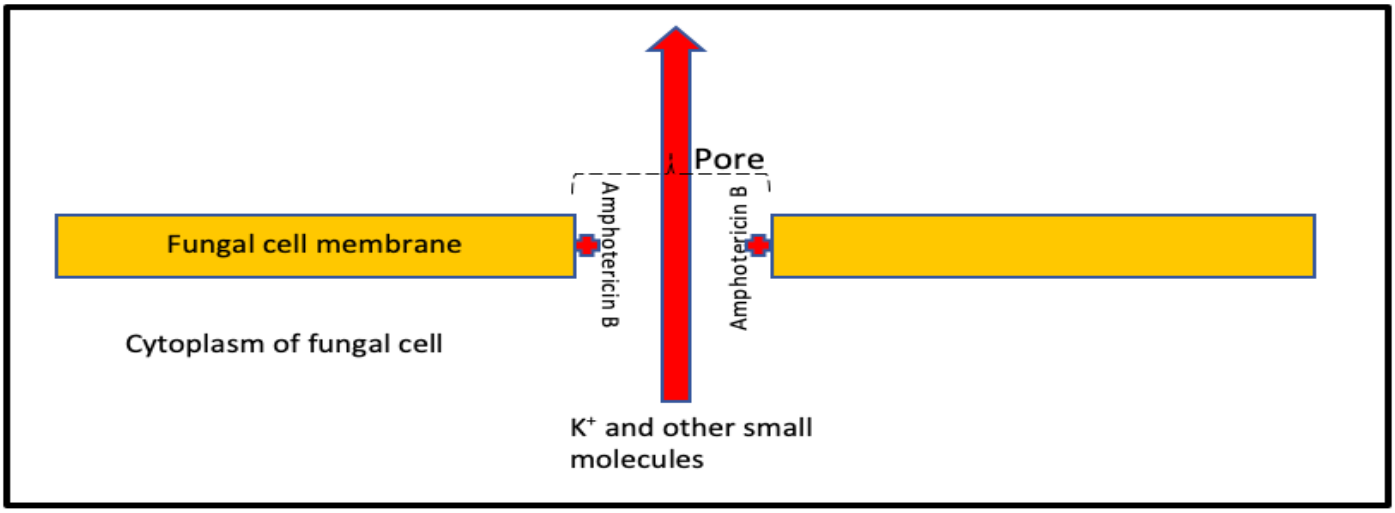

Figure 8: Mechanism of action of Amphotericin B. Amphotericin B hydrophobically binds to the sterol moiety of fungal cell membrane thereby creating pores/ channels. Loss of K^+ and other vital small molecules through these pores, lead to cell death

Its efficacy and uses are limited due to its poor penetration into CSF, saliva, bronchial secretions, pancreas, muscle, bone, vitreous humor, or normal amniotic fluid. It has useful clinical activity against *Candida*, *Cryptococcus*, *Blastomyces*, *Histoplasma*, *Sporothrix*, *Coccidioides*, *Paracoccidioides*, *Aspergillus*, *Penicillium* and Zygomycetes. *Candida lusitaniae* and *Aspergillus terreus* are 2 species that are often found to exhibit resistance to Amphotericin B[20]. However, hosts immune response is definitively a determinant factor in determining the outcome, especially in invasive Aspergillosis.

Various formulations of Amphotericin B, as C-AMB (Amphotericin B Deoxycholate), ABCD (Amphotericin B Colloidal Dispersion), ABLC (Amphotericin B Lipid Complex) and AMBISOME (Liposomal Amphotericin B) are available. ABCD, ABLC and Ambisome are Lipid Associated formulations of Amphotericin B. The indications, usage and side effects of each of these are distinctly different.

C-AMB, Amphotericin B-deoxycholate complex, forms a colloid in water. However, filters in infusion lines may remove significant amounts of the drug. Any addition of electrolytes to the infusion has been found to cause the colloids to aggregate.

ABCD , Amphotericin B Colloidal Dispersion contains equimolar amounts of Amphotericin B and cholesteryl sulphate.ABCD is less nephrotoxic than C-AMB, but has a higher

chance of causing fever and chills; therefore its administration as infusion over 3-4 hours, and use of premedication to reduce febrile reactions are advised. ABCD is approved only for patients with invasive Aspergillosis who are not responding to, or are unable to tolerate C-AMB. AMBISOME is a small unilamellar formulation of Amphotericin B that is supplied as lyophilized powder and is reconstituted for use, with sterile water. AMBISOME is approved for empiric therapy of fever in the neutropenic host not responding to appropriate antibacterial agents, as well as for salvage therapy of aspergillosis, cryptococcosis and candidiasis.
ABLC: Amphotericin B Lipid Complex. Blood levels of Amphoetricin B are much lower with ABLC than with a similar dose of C-AMB. It is approved for salvage therapy of deep mycoses.

IV Amphotericin B is the treatment of choice for mucormycosis, cryptococcal meningitis, severe or rapidly progressing histoplasmosis, blastomycosis, coccidioidomycosis, penicillosis marneffei and in patients not responding to azole therapy of invasive aspergillosis, extracutaneous sporotrichosis, fusariosis, alternariosis and trichosporonosis.
Intrathecal Amphotericin B is useful in patients with meningitis caused by *Coccidioides*.

Bladder irrigation with Amphotericin B is effective for Candida cystitis. Inhalational Amphotericin B is not a validated practice. However, an argument has been made that the aerosol might decrease *Aspergillus* infections in lung transplant recipients, including infections at the Broncho tracheal anastomotic site.

Echinocandins

Echinocandins act by inhibiting the synthesis of 1,3-ß-D-Glucan. 1,3-ß-D-Glucan, which provides much of the rigidity of the wall, is synthesized by a transmembrane glucan synthase complex[6]. Although the precise mechanism of action is unknown, echinocandins inhibit the functioning of this complex (Figure 9). They are fungicidal cyclic lipopeptides. Only intravenous formulations are available. Echinocandins are not active against *Cryptococcus neoformans* or *Trichosporonasahii*. Caspofungin, micafungin and anidulafungin are the 3 echinocandins currently in use[7]. The 3 echinocandins have essentially identical antifungal spectra with documented activity against all Candida species. It is effective against *Aspergillus* species; but is limited by the fact that it does not have any action on resting and dormant forms. Of the three, Caspofungin is the most studied and used, with a wide array of indications. Micafungin is mostly studied in pediatric age group including neonates. Anidulafungin has 2 important advantages over the other 2 in that it doesn't require dose adjustments in hepatic failure and elicits comparatively less drug interactions[22].

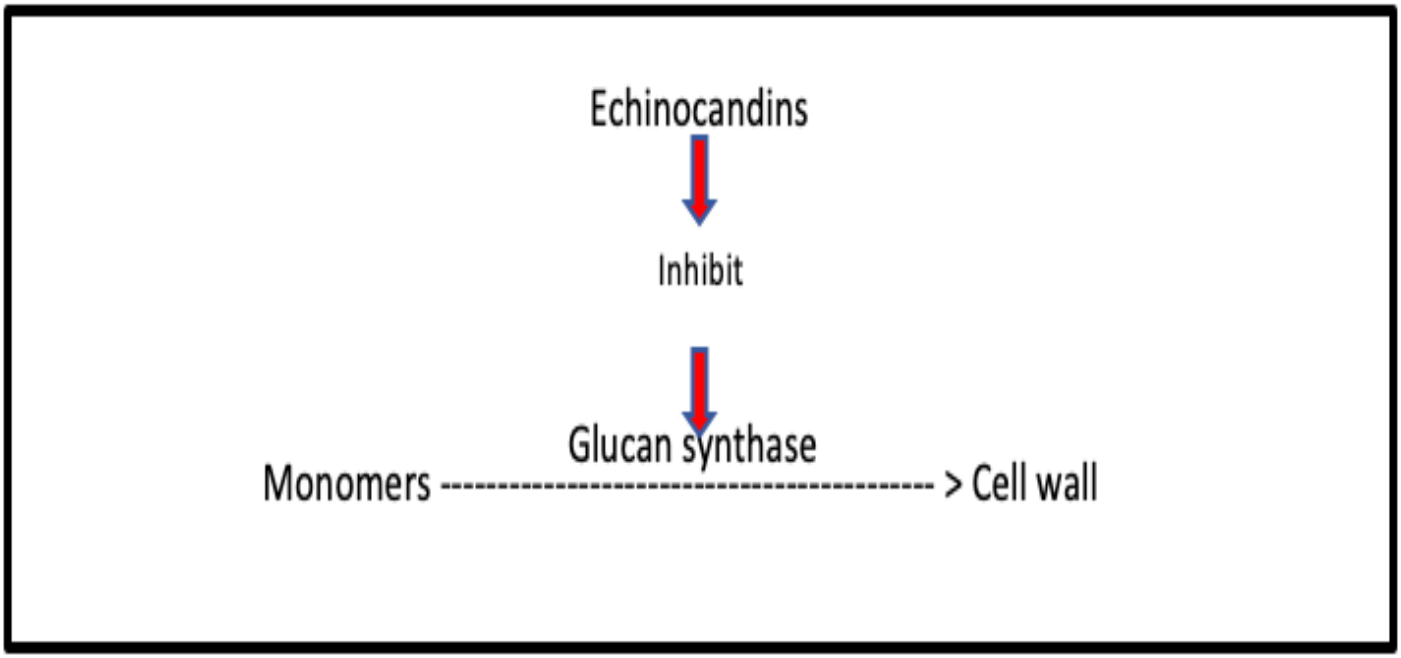

Figure 9: Echinocandins act on Glucan synthase complex, as a result of which fungal cell wall formation is blocked.

Triterpenoids

Triterpenoids is a novel class of structurally distinct glucan synthase inhibitors. Ibrexafungerp[23] is a much-awaited representative of the group. It holds much promise as it has documented activity against *Candida* including Multi Drug Resistant strains of *Candida Auris*, various *Aspergillus* species, as well as against *Pneumocystis jiroveci*. Its availability in oral and IV formulations offer broad use across OP and IP settings.

Investigational Antifungal Agents

Novel azoles, novel echinocandin-like compound, sordarins (acts on fungal elongation factors thereby inhibiting protein synthesis), nikkomycin Z (chitin synthesis inhibition), and various peptides with unknown mechanism of action[6]. Immunomodulators hold promise, but there is not available sufficient clinical data to comment on its efficacy.

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Special article

Vaccines in chronic respiratory diseases

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Vaccines play a significant role in preventing exacerbations of chronic respiratory diseases which are potentially life threatening. Vaccination is an important component in the rehabilitation of patients with chronic respiratory diseases. Thanks to routine childhood vaccination, the incidence of invasive Haemophilus influenza infection has dramatically declined across the country. Hence it is now time for us to shift our focus on to the adult populations who are at higher risk for vaccine preventable diseases, for example patients with chronic respiratory diseases, especially COPD. The aim of this analysis is to explore the scope of vaccines in this scenario.

Chronic respiratory diseases represent the third leading cause of death in United States out of which COPD is the most common cause. COPD is the fourth leading cause of death in the world and is projected to be the third leading cause by 2020. COPD accounts for 6% of all deaths globally and in terms of DALYs lost it has been ranked as the fifth leading cause. In India the prevalence of COPD is estimated to be 31-57% over 60 years of age. COPD exacerbations accounts for 40% of the total cost of COPD management, with a major portion attributable to hospitalisations[1-3].

The primary triggers of most exacerbations in COPD are community acquired respiratory infections caused by viral and bacterial pathogens[4]. Bacteria were believed to be responsible for most of the exacerbations until recently. But with the advent of PCR the actual prevalence of respiratory viruses has been realised. Around 70% of COPD exacerbations are infectious in origin, out of which 30% have been identified to be viral. Influenza has been identified as the second most common virus associated with COPD exacerbations, the first being rhinovirus[5]. Respiratory viruses specifically target airway epithelial cells leading to epithelial cell sloughing, micro vascular dilatation, oedema and immune cell infiltration. There is increased susceptibility to bacterial infection and impaired mucociliary clearance[5]. So, bacterial and viral co-infections can also occur, and secondary bacterial infection may complicate an initial viral infection[2]. Viral–bacterial co-infection, espe-

cially Streptococcus pneumonia occurring after influenza is an established phenomenon. Bacterial co-infection usually occurs within 6 days. Isolated viral infections and bacterial co-infections are clinically difficult to distinguish, but the latter has more severe outcomes. Influenza not only suppresses the immune response to streptococcus pneumonia, but also up regulates pneumococcal adhesion molecules. Influenza neuraminidase causes epithelial barrier dysfunction which further leads to increased bacterial adherence and proliferation[5].

Pathogen	Role in exacerbations (%)
Bacteria	
HaemophilusInfluenzae	20–30%
Streptococcus pneumoniae	10-15%
Moraxella catarrhalis	10-15%
Psuedomonasaeruginosa	5- 10%
Viruses	
Rhinovirus	10–25%
Influenza virus	5–10%
Parainfluenza virus	5–10%
RSV	5-10%
Adeno virus	3–5%
Corona virus	3–5%
Atypical Bacteria	
Chlamydophiliapneumoniae	3–5%
Mycoplasma pneumoniae	1–2%

Table 1: Common pathogens responsible for COPD exacerbations[7].

COPD patients have impaired mucociliary clearance and increased production of specific cell adhesion molecules that mediate attachment of bacteria and viruses to airway epithelium and thus are at increased risk of infections like influenza and pneumococcal pneumonia. A rapid decline in lung function and worse health-related quality of life are seen in patients with frequent exacerbations[6].Therefore, identifying evidence-based strategies like vaccinations, that prevent infections causing exacerbations of chronic respiratory diseases would have a significant impact on reducing the mortality and morbidity of this disease.

Pneumococcus

Streptococcus pneumonia, also known as Pneumococcus is encapsulated Gram-positive cocci. It causes variety of clinical diseases in both children and adults including otitis media, sinusitis, pneumonia, empyema and severe deep-seated diseases such as bacteraemia, meningitis, peritonitis, septic arthritis, osteomyelitis etc[4,8]. It often colonizes the nasopharynx of healthy children and adults and spreads as a result of extensive close contact. Patients with COPD frequently require inhaled and systemic corticosteroids for the treatment of exacerbations and this impairs the host antibody responses. Immunocompromised individuals, whether

congenital or acquired, are more prone to pneumococcal infection[4].

In adultse > 65 years, pneumococcal pneumonia was found to occur 7.7 times more commonly in chronic respiratory disease patients than in those without comorbidity. In Sweden severe/invasive pneumococcal disease (IPD) was found to occur two times more commonly in people with Asthma and 5 times more commonly in those with COPD or pulmonary fibrosis than in general population[9].

Pneumococcal Vaccination

Pneumococcal vaccination is recommended in COPD (Evidence level B) as per the GOLD guidelines for COPD[3]. The two pneumococcal vaccines recommended for adults are:

1) Pneumococcal polysaccharide vaccine (PPSV23) contains 25 microgram each of capsular polysaccharides from the 23 most commonly infecting pneumococcal serotypes and is marketed as PPSV23. Presently, PPSV23 contains capsular polysaccharides from pneumococci that are responsible for about 60 percent of all pneumococcal infection in adults. Pneumococcal vaccination induces a T-cell independent host response, producing antibodies via the B-cell response alone and thus does not induce immunologic memory. It is used in adults and children >2 years of age, but not in children <2yrs due to poor immunogenicity[4].

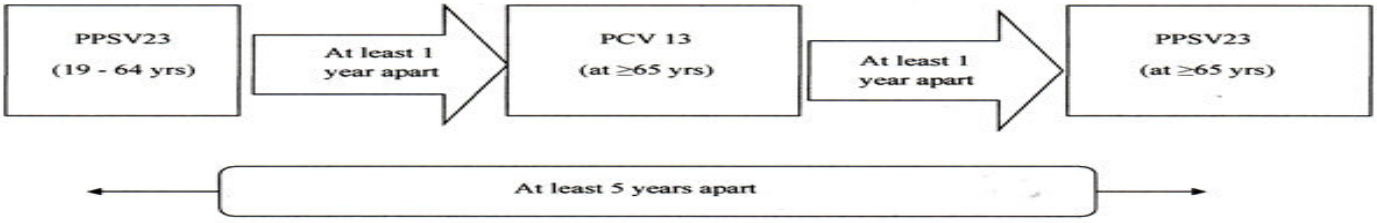
2) Pneumococcal conjugate vaccine (PCV) was introduced in the year 2000 for use in children. It was shown to prevent >90% of the invasive diseases caused by vaccine serotype. Initially marketed as PCV7, containing seven serotypes it was found to be an excellent immunogen in infants and toddlers and was hence adopted in their immunisation. In 2010, PCV7 was replaced by PCV13 containing 2.2 to 4.4 microgram each of 13 capsular polysaccharide types conjugated to a non-toxic variant of diphtheria toxin known as CRM197. It is highly effective in preventing otitis media in young children. Unlike PPSV23, PCV13 stimulates a T-cell-dependent host response, which does induce a memory immune response and is hence more immunogenic in paediatric patients. Interestingly, it has been seen that the widespread use of PCV among children has resulted in a 31% reduction in the rate of invasive pneumococcal disease in young adults and a 20% decrease in adults >65 years of age. Thus PCV clearly demonstrates herd immunity, leading to hopeful speculation that directly immunizing adults with a PCV13, instead of the currently available PPSV23, will result in better protection[4].

PCV13	PPSV23
Contain polysaccharide antigens covalently linked to a carrier protein	Contain polysaccharide antigens
Expensive	Not expensive
Enhanced immune response owing to the T cell dependent mode of action	Weaker immune response due to T cell independent mode of action
Better efficacy than PPSV23 in high-risk and elderly	Can provide protection against additional serotypes
Is approved for preventing IPD and pneumonia in adults > 50 years of age	Only prevents IPD
Potential efficacy in reducing nasopharyngeal carriage	No efficacy in reducing nasopharyngeal carriage
T cell-dependent immune response (larger duration and boosting effect at revaccination) Induces memory immune response.	Immune response declines in 3–5 years No anamnestic response at revaccination
Short experience	Long experience
Future reduction of vaccination impact in adults (because of herd immunity and probable indirect effects from PCV13 paediatric use)	Decrease in memory B cell frequency after PPSV23 Does not elicit long-lasting immunity[9]

Table 2 : Comparison of PCV13 and PPSV23 [9]

One dose of PCV 13 is recommended for adults:	• ≥65 years who have not previously received PCV 13. • ≥19 years with conditions like asplenia or immunocompromised states and who have not previously received PCV 13.
One dose of PPSV23 is recommended adults:	• ≥ 65 years, regardless of previous history of pneumococcal vaccination (once a dose of PPSV23 is given at ≥ 65 years, no additional doses should be given). • 19-64 years with conditions like asplenia or immunocompromised states.

Pneumococcal Vaccine shedule for adults with chronic respiratory diseases and smokers [11]



The above mentioned schedule is also recommended in patients with chronic heart diseases, chronic liver diseases, diabetes patients and also in chronic alcoholics[11].

Category	PCV13 for ≥19 years	PPSV23 for 19-64 years		PCV13 at ≥ 65 years	PPSV23 at ≥ 65 years
	Recommended	Recommended	Revaccination	Recommended	Recommended
Normal individuals (no comorbidities)				✓	✓ ≥ 1 year after PCV13
Immunocompetent persons with chronic respiratory diseases / cigarette smoking		✓		✓	✓ ≥ 1 year after PCV13 ≥ 5 years after any PPSV23 at < 65 years
Persons with functional or anatomical asplenia	✓	✓ ≥ 8 weeks after PCV13	✓ ≥ 5 years after first dose PPSV23	✓ If no previous PCV13 vaccination	✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years
Immunocompromised persons**	✓	✓ ≥ 8 weeks after PCV13	✓ ≥ 5 years after first dose PPSV23	✓ If no previous PCV13 vaccination	✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years

Table 3: indications for pneumococcal vaccines in adults [11]

***Immunocompromised persons include people with chronic renal failure, Congenital or acquired immunodeficiencies, Generalized malignancy, HIV infection, Hodgkin disease, Leukemia, Lymphoma, Multiple myeloma, Nephrotic syndrome, and those who have undergone solid organ transplantation[11]*

The sequential administration of PCV13 followed by PPSV23 one year later (PCV13/ PPSV23) have showed higher immune response, compared with PPSV23 followed by PCV13 one year later (PPSV23/ PCV13). Thus PCV13 is given first when both are to be given.[10] If either of the two vaccines is inadvertently given earlier, than the recommended schedule, do not repeat the dose. If a person has already received 1 dose of PCV13, do not administer an additional dose at 65 years or older. Both pneumococcal vaccines are administered as a 0.5 ml dose intramuscularly[11].

Contraindications

A previous history of anaphylaxis to vaccine components, pregnancy (women at risk of invasive pneumococcal disease should be vaccinated prior to pregnancy) [8].

Influenza

Influenza is an acute, febrile illness which is usually self-limited, transmitted mainly via respiratory droplets. However it can develop a severe disease with life-threatening complications especially in vulnerable populations such as older adults, very young children, pregnant women, and those with certain chronic diseases like COPD[4,13].

Influenza viruses belong to the Orthomyxoviridae family. The viruses are classified into three types—A, B, and C, of which only A and B cause respiratory diseases in humans. Influenza A is again classified into two subtypes according to the surface proteins Hemagglutinin (HA) and Neuraminidase (NA). It co-circulates in humans worldwide as H1N1 or H3N2 subtypes. Influenza B viruses also co-circulate and can be divided into two lineages, either B/ Yamagata or B/Victoria lineage. The distribution of the viruses varies from year to year and between geographic areas and time of the year[13]. The human influenza virus undergoes a slight genetic changes each year (antigenic drift) ,increasing risk of infection because of evasion of host immunity. More abrupt mutations in Hemagglutinin (H) and Neuraminidase (N), can lead to influenza epidemics because of creation of a new subtype of influenza virus to which most humans have no resistance (antigenic shift)[8]. Thus, influenza strains contributing to influenza epidemics vary annually , influencing the severity and length of each season[2].

Influenza vaccination is recommended in COPD (Evidence A) as per the GOLD guidelines[3].All Chronic respiratory disease patients require yearly influenza vaccination. Increase in vaccination uptake and early use of antivirals in COPD patients, will reduce influenza related hospital admissions and thereby improve health-care expense[14].

Groups recommended for Vaccination

Routine annual influenza vaccination is recommended for the following groups a who do not have contraindications[15].

- Children aged 6 through 59 months
- Adults aged ≥ 50 years
- Persons with chronic pulmonary diseases (including asthma),cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders(including diabetes mellitus)

- Persons who are immunocompromised due to any cause, including (but not limited to) medications or HIV infection
- Women who are or will be pregnant during the influenza season
- Children and adolescents (6 months -18 yrs) taking aspirin- or salicylate-containing drugs who might be at risk for Reye syndrome after influenza infection.
- Inmates of nursing homes and other long-term care facilities
- Persons who are extremely obese (BMI ≥ 40 for adults)
- Caregivers and contacts of those at risk

The ERS/ESCMID guidelines also recommend yearly influenza vaccination for the above mentioned groups[16].

Available Vaccines

1) Inactivated Influenza Vaccine (IIV): available as

a) - inactivated trivalent vaccine (IIV3) (including two influenza A and one B component)

b) -inactivated quadrivalent vaccines (IIV4)(including both influenza B lineages Yamagata and Victoria)

2) Recombinant influenza vaccine quadrivalent (RIV4)

3) Live attenuated influenza vaccines quadrivalent (LAIV4)

The LAIV4 or **Nasal** Spray Flu Vaccine available as a 0.2 ml prefilled intranasal sprayer, which is licensed in the United States from 2–49 years and in Europe from 2–18 years of age. Hence, it is an option for young COPD, non-pregnant patients. RIV4 is licensed for persons aged ≥ 18 years and should not be used for children aged < 18 years[15].

	IIVs and RIV4	LAIV4
Administration	Intramuscular	Intranasal
Contraindications	History of severe allergic reaction to vaccine or any of its components.	• History of severe allergic reaction to vaccine or any of its components. • Pregnancy • Concomitant aspirin or salicylate containing therapy in children and adolescents. • Immunocompromised patients / close contacts of severely immunosuppressed persons. • Receipt of influenza antiviral medication within previous 48 hours.
Precautions	• Moderate or severe acute illness ± fever • GBS within 6 weeks following a previous dose of influenza vaccine.	• Moderate or severe acute illness ± fever • GBS within 6 weeks following a previous dose of influenza vaccine. • Asthma in persons aged ≥5 years. • Other chronic medical conditions including respiratory diseases and diabetes that might predispose to complications attributable to severe influenza.

Table 4: Comparison of Influenza Vaccines[15]

IIVs - Inactivated Influenza Vaccines), RIV4 - Recombinant Influenza Vaccine , LAIV4 - Live attenuated influenza vaccine.

• **2019-20 Influenza Vaccines**

-contain hemagglutinin (HA) from influenza viruses antigenically similar to those recommended by FDA[15].

Trivalent vaccines will contain

- an A/Brisbane/02/2018 (H1N1)pdm09–like virus;
- an A/Kansas/14/2017 (H3N2)–like virus; and
- a B/Colorado/06/2017–like virus (Victoria lineage).

Quadrivalent vaccines will contain the same three HA antigens as trivalent vaccines, plus a B/Phuket/3073/2013–like virus (Yamagata lineage).

Timing of vaccination

- Vaccination should be offered by the end of October. But, vaccination should be offered as long as influenza viruses are circulating and unexpired vaccine is available.

Adults Aged ≥ 65 years

- ≥ 65 years may receive any age-appropriate IIV(standard- or high-dose, trivalent or quadrivalent, adjuvanted or unadjuvanted) or RIV4

Pregnant Woman

-An age-appropriate IIV or RIV4 may be used.

-LAIV4 should not be used during pregnancy.

-Influenza vaccine can be administered at any time during pregnancy.

Persons with Egg allergy

Individuals with a history of egg allergy of any severity may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4 or LAIV4)[15].

Diphtheria, Pertussis, Tetanus

Regular booster vaccination for diphtheria every 10 years is required, as it has been seen that a high proportion of immunised adults have antibody titres below protection level[13]. Pertussis has been recognized as a cause of significant morbidity in adults, even among people who where immunised in childhood, because immunity starts waning 4-6 years after vaccination.It is one of the less common causes of COPD exacerbations and shows a slight seasonality, with a modest increase in cases in the summer and autumn[16]. Pertussis in COPD patients is seen to be associated with increased morbidity and severe complications, like pneumonia, brain damage, seizures.

Tdap Vaccine: Whole cell pertussis vaccine has a protective effect in preventing allergic asthma and COPD exacerbations[17]. A Tdap dose is recommended if a COPD patient has not received a dose of Tdap during his lifetime. Hence, if Tdap recommendations by ACIP are incorporated into management of COPD and asthma, mortality and morbidity in these patients may be reduced[18]. A Td booster dose is recommended 10 yearly after that. It is given as a 0.5 ml dose intramuscularly. It is contraindicated in severe allergic reaction like anaphylaxis, after a previous dose of vaccine[13].

Herpes Zoster

Herpes Zoster incidence increases significantly with age and affects 50% of people who live to 85 years. Diabetes mellitus, COPD, cardiovascular diseases have been identified as risk factors for it. There occurs imbalances between subsets of CD8+ peripheral blood T cells, leading to impaired cell mediated immunity and this contributes to the pathogenesis of the immune response dysfunction in COPD[19].

Zoster (Shingles) Vaccine

Currently, two shingles vaccines have been licensed. Zoster vaccine live (ZVL) was used since 2006. It is a varicella virus–containing vaccine that reduces the risk of herpes zoster and also leads to reduction of post herpetic neuralgia. The vaccine is licensed to be given to persons>50 years and is given as a single 0.7-mL dose subcutaneously. Its protection starts waning after 5 years[13].

Recombinant zoster vaccine (RZV) is used since 2017 and is recommended by ACIP as the preferred shingles vaccine. RZV is the new adjuvanted, non-live recombinant shingles vaccine. Two doses of the vaccine provide >90% protection against shingles and post herpetic neuralgia. COPD patients > 50 years, should get the 2-dose series of RZV Shingles vaccine 2-6 months apart, even if already were vaccinated with ZVL. It is administered as 0.5 ml IM dose. It is contraindicated in patients with primary or secondary immunodeficiencies[20].

Vaccines in other chronic respiratory diseases

Out of the currently available vaccines those that can be given to bronchiectasis patients to decrease the incidence of exacerbations include vaccines for Streptococcus pneumoniae, Haemophilus influenza, Mycobacterium tuberculosis, Bordetella pertussis and influenza virus. In addition vaccines against Pseudomonas aeroginosa and RSV virus are in pipeline[21].According to BTS recommendations all bronchiectasis patients should be offered Polysaccharide pneumococcal vaccination and annual influenza vaccination[22].

Koji kuronuma et al found in their study that **ILD** patients who were immunized with PCV13 and PPSV23 had increased IgG concentrations. They also concluded that ongoing immunosuppressive and / or corticosteroid treatment did not affect the antibody response to pneumococcal vaccination, except in IPF patients[23].

Cystic fibrosis patients can clearly benefit from immunizations and they should follow national immunization programs without delay and in addition get immunized against HAV and HBV[24].Varicella vaccination is recommended at least for seronegative adolescents and candidates for transplantation.

Thus, in an otherwise fully immunized individual in childhood who develops chronic respiratory disease in adult life the ***pneumococcal, influenza, Tdap and zoster vaccines*** are indicated as a part of routine adult immunisation.

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Original article

Cardiac Troponin I in patients with exacerbation of chronic obstructive pulmonary disease

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Background: Cardiovascular co-morbidities and left ventricular dysfunction are common in chronic obstructive pulmonary disease (COPD). Retrospective studies suggest that cardiac troponin elevation is common during acute exacerbations of COPD. Some studies even showed poor survival in those patients.

Objectives: To investigate the prevalence of serum cardiac troponin I (cTnI) elevation in patients admitted to hospital with an acute exacerbation of chronic obstructive pulmonary disease (COPD).Secondary objective of the study was to find the correlation of cTnI with other laboratory parameters. We also aimed to find relationship between cTnI with mortality and duration of hospital stay.

Materials and Methods: It was an observational study, conducted in a tertiary care teaching hospital. Patients who presented with acute severe exacerbation of COPD were included in the study. Baseline demographics and other clinical data were collected. All the patients were subjected to the following investigations: serum cTnI measurement, laboratory investigations and other clinical parameters.

Results: Total 67 patients were included in the study. There were 58 (87%) males. cTnI elevation was observed in 43 of 67 (64%) patients. Despite the elevated cTnI result, univariate analysis did not show any statistically significant association with AECOPD mortality (P value: 0.303).There was no association between duration of hospital stay and cTnI too (P value 0.518) Other laboratory parameters like serum creatinine , CRP, and neutrophils were assessed for its correlation with cTnI and it showed correlation coefficient of 0.06, 0.03,and 0.172 respectively.

Conclusion: We conclude that 64% of patients with AECOPD had elevated cTnI. However, it was not associated with an increase in hospital mortality. We found there was positive correlation between elevated CRP, serum creatinine and increased duration of hospital stay.

Keywords: COPD, acute exacerbation, cardiac troponin I

Introduction:

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to the noxious particles or gases.[1] An exacerbation of COPD is an acute event characterised by worsening of patient's respiratory symptoms that is beyond normal day to day variations and leads to treatment modifications.[1] Cardiovascular risk factors and cardiac comorbidity are frequent in patients with COPD. Troponin elevation was found to be an independent predictor of the need for non invasive mechanical ventilation and mortality in patients who were admitted with acute exacerbation of COPD.[2-4] The amount of energy and oxygen needed for respiration is increased in the acute exacerbation period; in addition, the left ventricular afterload is increased in relation with more negative intra thoracic pressure. Worsened pulmonary hypertension, hypoxia, and hypercapnia also contribute to myocardial damage during the acute exacerbation period. These all may lead to elevated cardiac enzymes . The present study was designed to find out correlation between exacerbation of COPD and elevation of cardiac troponin I and its association with mortality and duration of hospital stay.

Materials and Methods:

The study was conducted at Amrita Institute of Medical Sciences, a tertiary care hospital in southern India. Study population consisted of patients admitted with AECOPD during the study period.

Inclusion criteria:

COPD was defined as GOLD guidelines for COPD. [1]

Definition of terminology:

AECOPD was defined as an increase in cough and dyspnea and as a change in sputum abundance and purulence. All the patients presenting with acute exacerbation of COPD were included.

Exclusion criteria:

Patients with diagnoses of asthma, sarcoidosis, interstitial lung disease, or neuromuscular disease were excluded. Patients with history of previous admission within one month of this admission were excluded. A proforma was prepared to collect clinical and laboratory details like age, sex, smoking status, duration of hospital stay, total white cell count, platelets,

c-reactive protein(CRP), troponin I levels and outcome.

All included patients were subjected to cTnI within the first 24 hours of admission. They were also subjected to other routine blood investigations like white blood cell count (WBC), hemoglobin concentrations (Hb), C-reactive protein, renal function test and liver function test.

The cTnI assay used by the hospital laboratory was Elecsys Troponin T STAT (Roche Diagnostics GmbH, Mannheim, Germany). cTnI was considered elevated at levels equal to or greater than 0.01 ng/l, at which point the assay has less than 10% coefficient of variation. Patients were subjected to arterial blood gas analysis as per treating physician's discretions. ECG was done for all patients at the time of admission and manually scored according to a Cardiac Infarction Injury Score (CIIS) algorithm modified for visual coding.[12]

Aims and Objectives

Primary objective was to find out correlation between trop I elevation and exacerbation outcome. Secondary objective was to find out correlation between trop I and other inflammatory markers as well as duration of hospital stay.

Statistical Analysis:

Chi-square test was used for between-group comparisons in univariate analyses on dichotomous variables (table 1). P value of <0.05 was considered statistically significant. Spearman correlation coefficient was used to find out correlation between cTnI and various variables. SPSS version 20 was used for statistical analysis.

Table 1: Base line demographics of study cohort

Character	*N* Median (Percentage/Range)
Age; in years	69 ± 10.19(43-91)
Sex Male Female	 58 (87) 09 (13)
Duration of hospital stay in days	7 ±4.031 (1-22)
Outcome Alive Dead	 58(87) 09(13)
Progression free survival	5162 (9-883)
Trop I Not elevated: (>0.014) Elevated : (<0.014)	0.014±0.302 24(36) 43(64)
Other lab parameters Urea Creatinine CRP ESR Total White cell count Neutrophils Platelets	 38±23.34 1.07 ± 1.24 25 ±83.78 30±16.48 11.5±5.71 79.7±11.37 293±109

P value of <0.5 was considered by statistically significant. Spearman correlation coefficient was used to find out correlation between cTnI and various variables. SPSS version 20 was used for statistical analysis

Table 2: Univariate analysis of different variables with outcome and duration of hospital stay

Variable	Response *n*=58, 5 patients' data NA		Duration of Hospital stay Odd's ratio(95% CI) P value	Outcome Odd's ratio(95% CI) P value
	Survivor	Non-survivor		
Sex				0.845
Male	49	9	0881	(0.757-0.943)
Female	9	0	(0.199-3.892)	0.249
			0.591	
Trop I				
<0.014	22	02	0.833	2.139
>0.014	36	07	(0.316-2.520)	(0.407-11.233)
			0.518	0.303
S creatinine				
<1.07	53	07	0.691	3.029
>1.07	05	02	(0.123-3.865)	(0.491-18.681)
			0.511	0.235
CRP				
<25	49	07	1.623	1.556
>25	09	02	(0.438-6.011)	(0.277-8.728)
			0.344	0.457
Age				
<69	29	04	0.736	1.250
>69	29	05	(0.270-0.004)	(0.305-5.130)
			0.365	0.520

Table. 3 Correlation of trop I with other variables

			tropi	age	creat	crp	tcf	neutroph	durofhs	durhsf	outcome
Spearman's rho	tropi	Correlation Coefficient	1.000	.074	.068	.036	.103	.172	.034	-.006	.129
		Sig. (2-tailed)	.	.552	.587	.794	.408	.163	.786	.959	.297
		N	67	67	67	56	67	67	67	67	67
	age	Correlation Coefficient	.074	1.000	.157	-.114	.091	-.050	-.183	-.205	.016
		Sig. (2-tailed)	.552	.	.205	.403	.463	.690	.139	.097	.899
		N	67	67	67	56	67	67	67	67	67
	creat	Correlation Coefficient	.068	.157	1.000	.277*	.235	.082	-.233	-.164	.033
		Sig. (2-tailed)	.587	.205	.	.039	.056	.509	.057	.186	.792
		N	67	67	67	56	67	67	67	67	67
	crp	Correlation Coefficient	.036	-.114	.277*	1.000	.215	.083	.004	-.016	-.120
		Sig. (2-tailed)	.794	.403	.039	.	.112	.541	.977	.908	.378
		N	56	56	56	56	56	56	56	56	56
	tcf	Correlation Coefficient	.103	.091	.235	.215	1.000	.328**	.000	.073	-.038
		Sig. (2-tailed)	.408	.463	.056	.112	.	.007	1.000	.555	.761
		N	67	67	67	56	67	67	67	67	67
	durofhs	Correlation Coefficient	.034	-.183	-.233	.004	.000	-.002	1.000	.837**	.131
		Sig. (2-tailed)	.786	.139	.057	.977	1.000	.987	.	.000	.290
		N	67	67	67	56	67	67	67	67	67
	durhsf	Correlation Coefficient	-.006	-.205	-.164	-.016	.073	.039	.837**	1.000	.071
		Sig. (2-tailed)	.959	.097	.186	.908	.555	.751	.000	.	.569
		N	67	67	67	56	67	67	67	67	67
	outcome	Correlation Coefficient	.129	.016	.033	-.120	-.038	-.088	.131	.071	1.000
		Sig. (2-tailed)	.297	.899	.792	.378	.761	.477	.290	.569	.
		N	67	67	67	56	67	67	67	67	67

*Correlation is significant at the 0.05 level (2- tailed)
**Correlation is significant at the 0.01 level (2- tailed)

Results:

The mean age of the cohort was 69 yrs and 13% were female. Only 17 (25%) of the patients had never smoked. Spirometry data was available for very few patients so was not included in analysis. The median Trop I value was 0.014±0.302. Out of 67 patients, 9(13%) did not survive. Median duration of hospital stay was 7 ±4.031 (1-22) . Baseline characteristics for the cohort are shown in Table 1. Univariate analysis was done to find out association of cTnI and other variables with duration of hospital stay and overall survival which is shown in

table 2. Table 3 shows the spearman correlation of Trop I with other variables and outcome. There was statistically significant correlation between Trop I and CRP, and increased duration of hospital stay if there was elevated trop I. There was borderline correlation between age and elevated Trop I as well as creatinine but not amounting for statistically significant level.

Kaplan Meier Survival curve was plotted for Trop I and cumulative survival. It is shown in fig 1. However, it did not show statistically significant correlation between elevated cTnI and survival.

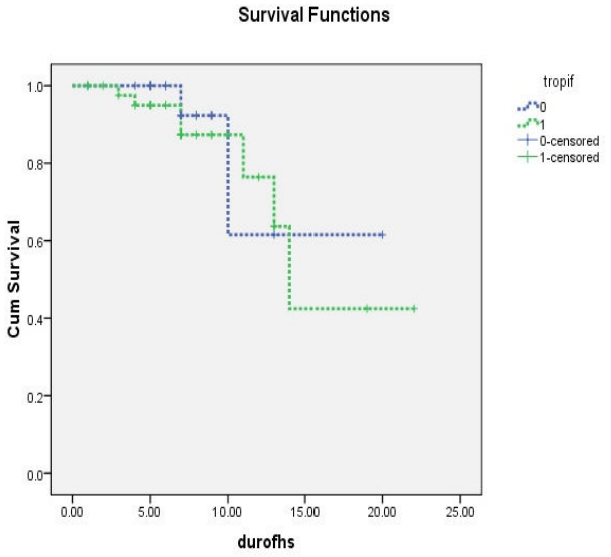

Fig: 1 Showing Kaplan Meier survival curve, survival according to cTnI of the patients: Trop I < 0.014:, Green and > 0.014 (blue)

Discussion

COPD is a chronic inflammatory disease that promotes atherogenesis and CHD.[5] During acute exacerbations, hypoxemia and stress associated with increased work of breathing may promote sympathetic overactivity that increases myocardial oxygen demand[6-8]. Accordingly, myocardial ischemia and left ventricular dysfunction, which itself can promote wheezing, may complicate or be mistaken for an exacerbation of COPD. Tachycardia, hypoxemia and dilatation of the right ventricle often seen in COPD exacerbations, and complications such as pulmonary arterial hypertension, are all factors that may cause troponin release [7-8].There is increasing awareness of IHD as a major contributor to morbidity and mortality in the present patient population [8-11].

The diagnosis of COPD was based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. The overall mortality rate being 13% in the present study was comparable with the long-term mortality rate in previous studies of patients hospitalised with COPD exacerbation [13-14].

Our study cannot decipher whether ischemia is the primary reason for dyspnea, or a stress-related complication that contributes to dyspnea in this vulnerable cohort. In the present study we found that cTnI was elevated in 43 (67%) of 67 patients with AECOPD. ECHO was

not done in all patients, however ECG changes for myocardial infarction were ruled out in all the patients.

The majority of patients were current or former smokers, and were at increased risk of developing other smoking-related diseases. It is proven that troponin release is seen in COPD even in patients with normal coronary arteries on angiography [12] ,this does not preclude the possibility that many COPD patients actually have underlying quiescent IHD.

Serum Creatinine was done for all the patients. The spearman correlation showed borderline correlation between both with coefficient value 0.06. Other inflammatory markers like CRP showed correlation coefficient of 0.03.Previous study also have shown this. [15]

We found that elevated cTnI was not a strong risk factor for mortality in AECOPD. Some of the studies have shown the correlation between increased mortality and AECOPD. The smaller size of the study may be the reason for results not showing statistically significance. However, it may be important for risk stratification and treatment of patients hospitalised for COPD exacerbation.

Limitations

One obvious limitation of the present study is the smaller sample size. Even though our study concluded that Trop I value did not influence the association between cTnI and mortality among these patients. Still, the conclusions drawn from the present study should be considered as hypothesis generating.

Conclusion

We conclude that 64% of patients with AECOPD had elevated cTnI. However, it was not associated with increased in hospital mortality. We found there was positive correlation between elevated CRP, serum Creatinine and increased duration of hospital stay.

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Radiology Pearl

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A male patient in his thirties presented with left sided chest pain and blood-stained sputum. He was a nonsmoker with no history of tuberculosis nor any history of exposure to asbestos. He gave a history of left lower lobectomy for bronchiectasis. As the chest X ray and CT thorax lesion was suggestive of a mass, bronchoscopy was done which yielded only necrotic tissue, So a CT guided biopsy was done .It showed chronic inflammatory cells with no evidence of malignancy.

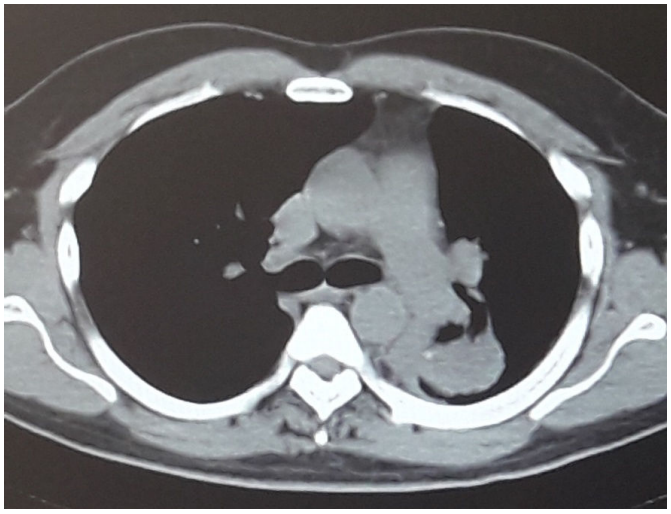

Fig 1

What is this condition and what is the radiological sign called?

Answer:

'Comet tail' sign (Blesovsky's syndrome)

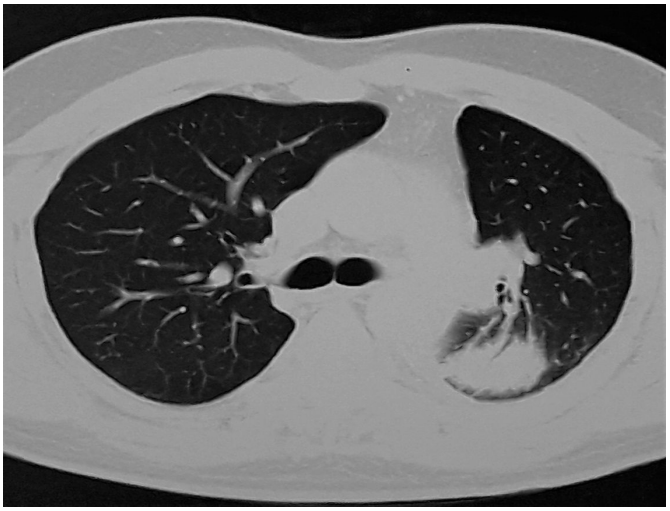

Fig 2 The mass which produced the Comet tail sign could be due to folded pleura. The patient became asymptomatic and is not willing for another surgery.

The **comet tail sign** is seen on CT scans of the chest and consists of a curvilinear opacity that extends from a subpleural "mass" towards the ipsilateral hilum. Distortion of vessels and bronchi that lead to an adjacent area of round atelectasis lead to the comet tail appearance. The dis-

torted bronchovascular bundles appear to be pulled into the mass and thus resembles comet tail[1,2]. The sign is due to contracted fibrous scarring and shrinking pleural disease with rounded atelectasis.[3,4].

The curvilinear shadows probably reflect the mechanical distortion of the lobe produced by the forcible contraction of the outer pulmonary surface attached to the relatively fixed hilum, resulting in compression of pulmonary tissue along the lines of the intralobar septa[5].

Though asbestosis is found to be the commonest association with comet, it may also be seen in following trauma, pulmonary infarction, pneumonias or rarely as an incidental finding on Chest X-ray.Patients with chest pain may require thoracotomy with removal of the visceral pleura and release of the folded lung which often result in symptom resolution[6].

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Radiology Quiz

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Case summary

A 62 year old gentleman with systemic hypertension, type 2 diabetes mellitus and chronic kidney disease presented to the internal medicine outpatient department with dysphagia and cough for 3 months duration. After initial evaluation by physician, he was subjected to a chest radiograph posteroanterior view, which is shown below. (Fig 1) Pulmonology consultation was sought and a C T scan of the chest was requested, the representative images of which are given below. (Fig 2a, 2b, 2c) A barium swallow was also ordered, the image being attached. (Fig 3)

What is the diagnosis?

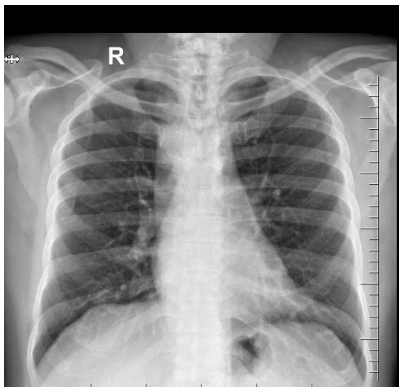

Fig 1 – Chest radiograph – PA view

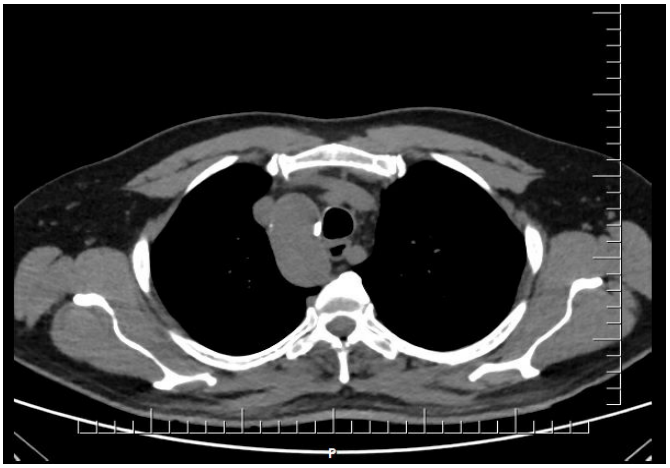

Fig 2a,

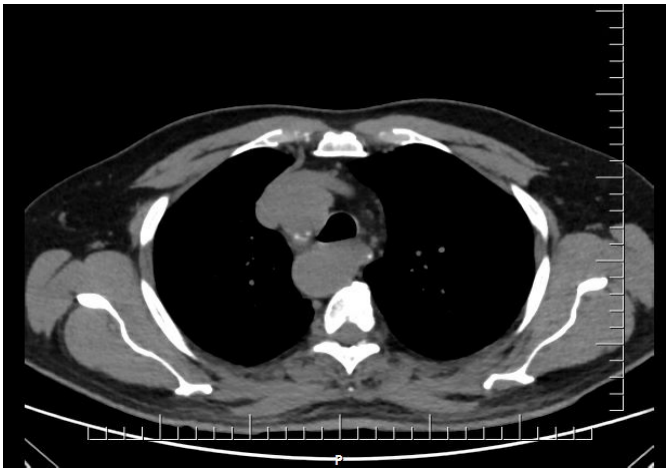

Fig 2b . Representative images of CT scan of thorax

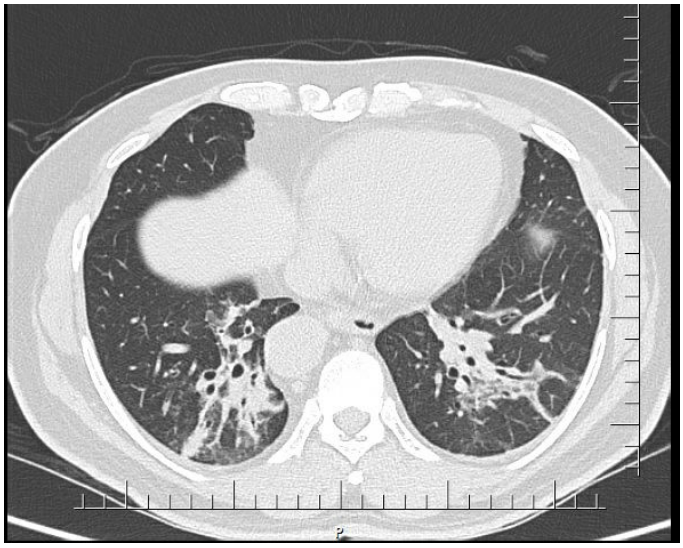

Fig 2c .

(Fig 2a,2b and 2 c . Representative images of CT scan of thorax)

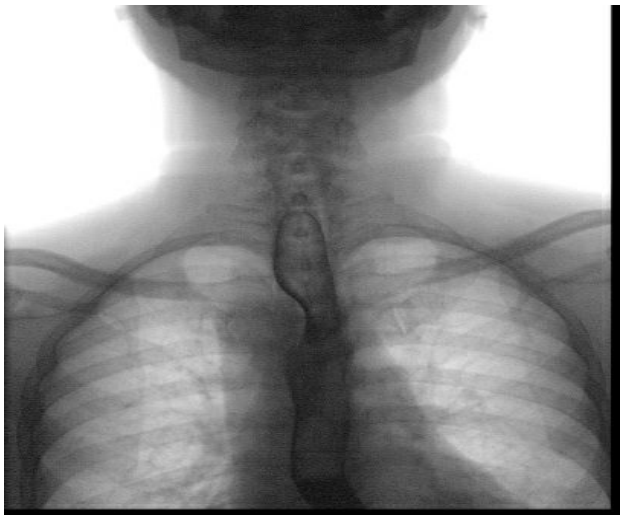

Fig 3 – Representative image of barium swallow

Answer

Kommerell's diverticulum

Right sided aortic arch with aberrant left subclavian artery; aneurysmal dilatation of origin of the aberrant left subclavian artery at the junction of right aortic arch and right descending thoracic aorta compressing the esophagus and trachea

Discussion

The postero anterior chest radiograph (Fig 1) shows a right sided aortic arch and bilateral lower zone alveolar shadows. The CT thorax – mediastinal window cuts (Fig 2a and 2b) show a right sided aortic arch with an aberrant left subclavian artery along the posterior aspect of esophagus. The origin of the left subclavian artery shows a bulbous dilatation measuring about 2.6 cm which is compressing and intending the mid esophagus and posterior wall of trachea. The lung window cuts (Fig 2 c) show patchy fibrosis with bronchiolar dilatation in bilateral lower lobe posterior basal segments and patchy ground glass opacities involving the lower lobes. Contrast study would have been optimal, but was not undertaken as the patient had chronic kidney disease and risk of contrast induced nephropathy was high. The overall picture is consistent with a right sided aortic arch, aberrant left subclavian artery origin - Kommerell's diverticulum, compressing the mid esophagus as well as trachea and features of chronic aspiration. Barium swallow images (only one image depicted - Fig 3) showed features of extrinsic compression of proximal thoracic esophagus on its posterior and right aspect causing mild luminal narrowing.

Kommerell's diverticulum is an uncommon congenital thoracic vascular anomaly characterized by aneurysmal dilatation of the aortic arch. The condition was first reported by Burckhard F. Kommerell in 1937 in a patient with left sided aortic arch and right aberrant subclavian artery[1]. Since then, multiple case reports, case series and review articles have been published. More common presentation is with right aortic arch and left aberrant subclavian artery[2]. The diverticulum represents a remnant of the primitive distal left aortic arch and is situated at the junction of the right aortic arch and the right descending aorta. In these cases, the course of the aberrant subclavian artery is usually posterior to the esophagus(80% of cases) but other possibilities have also been described. The subclavian artery can also pass between the esophagus and the trachea (15% of cases), or anterior to the trachea (5% of cases). Sometimes, a left ligamentum arteriosum situated between the left subclavian artery and the left pulmonary artery forming a vascular ring.

Kommerell's diverticulum is generally asymptomatic and diagnosis is often incidental. Even in situations of formation of a vascular ring, the ring is usually loose and does not cause severe symptoms of tracheal or esophageal compression. However, dysphagia due to esophageal compression and cough due to tracheal compression has been reported in literature[3].

Multidetector CT angiography is the investigation of choice for diagnosis of the condition[2]. The acquired image scan be reconstructed and viewed from different angles, which simplifies location, identification and size estimation. The spatial relationships between a diverticulum and surrounding structures are also well depicted which is crucial to detect compression of the esophagus or trachea by either the diverticulum itself or a vascular ring of patients who are symptomatic. 4 different types of Kommerell diverticulum are reported in the literature,[4, 5] the one with right aortic arch and aberrant left subclavian artery being the commonest.

The treatment of asymptomatic or mildly symptomatic Kommerell diverticulum is controversial. Case reports and case series advocate surgical corrective approaches as the risk of rupture is high. Surgical indications however have not been well established due to the rarity of the condition. Primary indication in one series was the diameter of Kommerell's diverticulum, surgery being contemplated when this was more than 50 mm[6]. Such patients were more likely to have symptoms associated with Kommerell's diverticulum. Core components of surgical repair are the resection of Kommerell's diverticulum and the reconstruction of the

aberrant subclavian artery. Endovascular treatment modalities have also emerged, given the complexity and expertise needed for surgical repair.

Our patient had mild to moderate symptoms with features of chronic aspiration and would have benefitted from surgical correction. However, he opted out of surgical treatment given the risks involved in the procedure. He was given symptomatic treatment and continues to be in clinical follow up.

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Pulmon is now Indexed

We are happy to inform you all that Pulmon is now indexed in Index Copernicus. On this occasion we thank the past editors, the past and current office bearers and governing council members of APCCM, those enriched the journal with articles, members and well wishers of APCCM whose relentless efforts made this remarkable achievement possible. Saluting the founder editor Late Dr.R.C.Babu for his far sighted vision even during the infancy period of the journal. We request all to continue your patronage and support.

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Self assessment quiz

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Question A: Which of the following is **NOT** a symptom of hypercapnia?

1. Fatigue
2. Headache
3. Hyperventilation
4. Flushing
5. Dizziness

Answer 3. Hypoventilation leads to hypercapnia[1]. Hyperventilation will lead to carbon dioxide washout and hypocapnia. Hypercapnia will lead to a variety of symptoms which are usually non specific. Any one or more of the following symptoms in a patient who is at risk to develop hypercapnia should alert the physician to evaluate and order for arterial blood gas analysis to rule out hypercapnia. These symptoms include flushing of the skin, dizziness, excessive fatigue, headache, disorientation, dyspnea, drowsiness, confusion, depression or paranoia, irregular heartbeat, panic attacks[1]. In severe cases muscle twitching, coma and seizures can occur[1].

Question B: Which of the following is the **MOST COMMON** cause for hypercapnic respiratory failure?

1. Obstructive sleep apnoea
2. Degenerative neuromuscular disorders
3. Chest wall deformities
4. Acute exacerbation of COPD
5. Acute severe Asthma

Answer: 4. All of the above conditions can lead to hypercapnic respiratory failure but worldwide most common cause is acute exacerbation of COPD[2].

Question C: Which of the following is **LEAST LIKELY** to cause lethargy in a COPD patient?

1. Hypercapnia
2. Hyperthyroidism
3. Hyponatremia
4. Polycythemia
5. Depression

Answer 2. One of the most important symptoms of hypercapnia in a COPD patient is lethargy. Hypothyroidism, not hyperthyroidism can lead to lethargy. Above are the other common conditions which can coexist in a COPD patient, which can also lead to lethargy[3].

Question D: Which is **NOT** a feature of untreated hypercapnic respiratory failure?

1. Paradoxical respiration
2. Poor effort while breathing
3. Excess sweating
4. Bounding pulse
5. Normal oxygen saturation

Answer 5. Hypoventilation is the basic cause for hypercapnia. Hence untreated hypercapnic respiratory failure is always associated with low oxygen saturation[2].

Question E: A 16 year old boy admitted following an accident is found to have hypercapnic respiratory failure. Which of the following is **LEAST LIKELY** to be the cause for his hypercapnia?

1) Lung contusion
2) High spinal cord injury
3) Head injury
4) Upper airway obstruction
5) Opioid over dose

Answer 1. Lung contusion will lead to hypoxia and may lead to hypocapnea due to hyperventilation. High spinal cord injury and head injury can lead to hypercapnia due to respiratory muscle dysfunction. Opioid over dose can lead to hypercapnia due to central respiratory depression. Upper airway obstruction is a rare cause for hypercapnia, is not uncommon following accidents. This should always be considered when there is no other obvious cause for hypercapnia. Patient may have other features of upper airway obstruction. Acute upper airway obstruction with hypercapnia is potentially fatal if not diagnosed and treated promptly.

Question F: Which of the following is **NOT** a cause for persistent hypercapnia in a patient on non invasive ventilation?

1. Inadequate bronchodilators
2. High respiratory rate
3. Patient ventilator asynchrony
4. Improper ventilatory settings
5. Improperly fitting mask

Answer 2: High respiratory rate will lead to carbon dioxide wash out and hypocapnea[4].

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Case report

Diagnosing pulmonary embolism in a high risk patient - Tracking the wrong steps

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Abstract

Pulmonary embolism is a common cause of breathlessness in post-operative ward, especially in oncology settings. However, inappropriate screening or investigations may underdiagnose its occurrence. We present a case of pulmonary embolism which was initially missed on initial examination. Once the flaws in the approach were identified, we could successfully identify the underlying pulmonary embolism and thus treat the patient, thereby avoiding further catastrophe. This case emphasizes on the need and utility of a structured approach to patients with pulmonary embolism, and not to be carried away by random investigation results

Keywords : Pulmonary Embolism, Algorithmic approach

Pulmonary thromboembolism has been recognized as one of the leading cardiovascular killers after stroke and myocardial infarction. Immobilsation following surgery or trauma, malignancy, cancer chemotherapeutic are the major risk factors for thromboembolism[1]Cancer patients have a 6-fold increased risk of venous-thrombo-embolism (VTE) versus non-cancer patients[1]. VTE in cancer patients is has its own ominous importance as demonstrated by Bura et al[2]. Deep vein thrombosis is common in patients with diagnosed cancer, and can also be the first warning sign of an occult cancer in as much as 26% of patients[2].

Untreated, pulmonary embolism has mortality rates as high as 26–30%, that comes down to a rate of 2–8% in treated patients[3]. This data, although based on low quality evidence, (small studies with major limitations), emphasizes the need of prompt diagnosis and appro-

priate management. There is no ambiguity in the management of patients presenting with hemodynamic instability and pulmonary embolism or the other extreme of minimal risk pulmonary embolism. However it may be difficult to diagnose and treat patients presenting with sub massive pulmonary embolism and stable hemodynamics. A clinical algorithm that includes a screening for pre-test probability may help to pick up pulmonary embolism especially if its sub massive embolism[4]. Here we describe a case in which we went wrong in many steps, but were fortunate to nail the diagnosis.

Case history

A 66-year-old female, previously diagnosed as a case of Carcinoma left buccal mucosa, and tongue in 2013 presented with suspicious lesion on left lateral border of tongue. She was taken up for tumor excision with reconstruction and tracheostomy after routine preanesthetic work up. Intra operative and immediate post operative period was uneventful. However,4 days down in the post operative period in ward, she developed respiratory distress and desaturation. She was seen by the duty doctor who did tracheostomy suctioning, and started oxygen via Tracheostomy tube. Bed side ECG was normal, except for tachycardia. A D-dimer was asked for and as the patient did not improve with oxygen she was referred to High dependency unit.

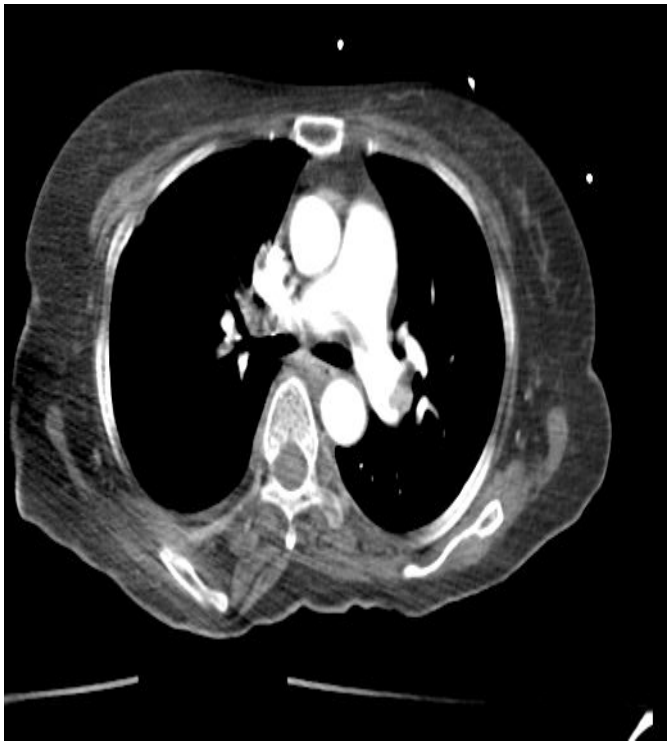

Fig 1; - CT Angiography showing embolus in left main pulmonary artery.

On arrival to ICU, patient was tachypnoeic, with a respiratory rate of 30, heart rate of 105 and blood pressure of 110/68. Her saturation on room air was 90%. Her chest was clear, with no added sound. The Icu registrar started oxygen @ 4 liter per minute via t piece and did tracheostomy suctioning. A screening echo revealed normal function and size of both RV and LV. A 4-point compression ultra sound revealed no evidence of DVT. A chest x ray taken was also normal with no obvious abnormalities. The patient improved gradually with tachycardia and tachypnoea settling to normal levels, and within the next 12 hours, she was gradually weaned off oxygen. The d dimer sent from

the ward was traced and found to be 630 (latex immunoturbidimetric method). Low molecular weight heparin was added as DVT prophylaxis, and as she was clinically stable, she was shifted to ward with a provisional diagnosis of tracheostomy tube blockage.

Incidence of pulmonary embolism in cancer patients and in post operative opatients

The incidence of VenousThromboembolism is around 1 of 200 with maximum incidence being noted with that cancers of the pancreas, lung, and stomach, and adenocarcinomas of unknown primary[5]. The patients with a combination of thrombosis and cancer have a lower survival rate than those with cancer alone probably explained by death due to thromboembolism or aggressive malignancies[5].Surgery in these group of patients doubles the risk of postoperative venous thromboembolism and nonfatal pulmonary embolism (PE) and triples the risk of fatal PE, despite thromboprophylaxis[6].

Probability assessment for pulmonary embolism

The first step in assessing a patient with suspected pulmonary embolism is to assess the risk of the patient for the same. The clinical signs and symptoms of pulmonary embolism are very nonspecific and misleading[7].However, if they are analyzed in a systematic way, according to the prediction scores available, the sensitivity and specificity to predict the probability of pulmonary embolism are very high and subsequent need for further investigations are guided by these. The post-test probability of Pulmonary embolism depends both on the characteristics of the diagnostic test and on the pre-test probability. So, this step should become a key step in all diagnostic algorithms for PE, desapite of its cumbersome nature. There are many scoring systems like Geneva and Wells scoring system and their positive predictive and negative predictive values are similar[8].

Routine Trans Thoracic Echocardiography in Screening for Pulmonary Embolism.

In hemodynamically unstable patients, echocardiography may help in diagnosing acute RV overload or other causes of hemodynamic instability. Echocardiographic findings associated with RV dysfunction include RV dilation with an increased RV–LV ratio, hypokinesia of the free wall of RV (McConnel's sign), decreased tricuspid annulus plane systolic excursion, or combinations of the above. However, in hemodynamically stable patients, echocardiographic examination is not recommended as part of the diagnostic work-up. The negative predictive value for echocardiography in Pulmonary embolus is 40 – 50% and the signs of RV overload or RV dysfunction are not pertaining only to pulmonary embolism[9]. A recent meta-analysis

assessing the diagnostic ability of TTE in diagnosing pulmonary embolism found that although TTE had a high specificity of 83%, the sensitivity in diagnosing pulmonary embolism was only 53%[10]. These data suggest that bed side echocardiography may be used to diagnose pulmonary embolism in hemodynamically unstable patients but does not rule out pulmonary embolism, especially if hemodynamically stable. In patients with proven pulmonary embolism, the tricuspid annulus plane systolic excursion (TAPSE) appears to be the best marker with minimal inter observer variability and values less than 15 mm, helps in better risk stratification for patients with an increased risk of 30-day mortality.[11, 12.]

D dimer in Pulmonary embolism

D dimer assay by Elisa are the reference standard for D-dimer quantitation. They have high sensitivity, specificity and high negative predictive value that helps to rule out PE in low risk cases. As fibrin may be excessively produced in cancer, a positive value may not be useful to rule in pulmonary embolism, especially in patients with malignancy. ELISA assays are expensive, labor intensive, and time consuming and has been replaced by latex derived agglutination assays and latex based immunoturbidometric assays. However, the use of these diagnostic tests in a clinical algorithm has not yet make its way into international guidelines or recommendations. Thus, the practice guidelines by American College Of Physicians suggest using D-dimer tests only for those at intermediate or low risk for a pulmonary embolism. They recommend that D dimer testing should be avoided in patients at high risk for pulmonary embolism as a negative D-dimer test will not eliminate the need for further imaging[1].

Incidental PE (IPE) and cancer

The frequency of Incidental pulmonary and venous embolism in oncology patients are increasing in view of the increased diagnostic interventions and diagnostic performance of MDCT. Incidental pulmonary embolism has a prevalence of 2.6%, with a higher prevalence in patients with malignancy (3.1%) and hospitalization. (4.0%)[1]. Although detected incidentally, many patients with IPE and malignancy will have symptoms of pulmonary embolism, which were atributed to other causes such as ageing, malignancy and cachexia of malignancy, and toxicity of chemotherapy. However, it must be kept in mind that CECT done for routine investigation of malignancy has a high false positive rate for sub segmental pulmonary embolism and low inter observer agreement. The incidental pulmonary embolism is significant clinically as postmortem studies have reported incidental PE a frequent and unrecognized cause

Table 1:- Table comparing sensitivity, specificity, positive and negative predictive value for various scoring systems used in pulmonary embolism[8]

Clinical score	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Revised Geneva score	0.54	0.29	0.75	0.71
Wells score	0.67	0.53	0.7	0.64
Simplified wells score	0.92	0.18	0.61	0.6
Pisa model	0.71	0.82	0.85	0.67

forming a pulmonary angiogram will not be practical due to the risks of contrast, and radiation exposure and costs involved. A compression ultrasound of the lower limbs might detect incidental VTE that strengthens the need for treatment. The ISTH guidelines recommend initiation of anticoagulation therapy after due consideration of the bleeding complications after discussion with patients and caregivers. A minimum of 3 – 6 months of anticoagulation is recommended, preferably using LMWH[16].

It seems prudent to treat patients with symptoms suggestive of PE and having incidentally detected PE, patients with IPE in main branches of pulmonary vasculature, and patients with incidental sub segmental PE and associated DVT.Regarding the duration and treatment of solitary sub segmental pulmonary embolism, the guidelines remain inconclusive and probably a 3- 6 months anticoagulation will suffice.

In our case, as the patient improved with symptomatic measures, and as the echocardiography, compression ultrasound and age adjusted D- dimer was negative, she was sent to ward after observation in ICU. However, going by the prediction for PE, we can see that she is having a PE likely risk. In those with substantial risk for PE the investigation of choice is CT pulmonary angiography and as she had a high probability of PE in view of age, tachycardia, recent surgery and malignancy,

echocardiography and D dimer, would have only a low positive predictive value and were wrong investigations in the current scenario.She was asked to perform a CT pulmonary angiogram which revealed embolus in bifurcation and left pulmonary artery. She had no venous thrombosis on Doppler screening. She was initiated on anticoagulation with LMWH and was asked to remain under follow up in the thrombosis clinic also.

This case underlines the significance of assessing pre-test probability of pulmonary embolism in patients and choosing the appropriate diagnostic modality for diagnosing and treating pulmonary embolism in suspected cases.

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Case report

An unusual case of Pleural Effusion

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Abstract

Angiomyolipomas of the mediastinum are extremely rare. Herein we report the case of a young lady who presented with left sided massive pleural effusion, which on detailed evaluation was found to be due to anterior mediastinal angiolipoma. To the best of our knowledge this is the first case of mediastinal angiolipoma with pleural effusion to be reported from India.

Key words: mediastinal angiomyolipomas

Introduction

An angiomyolipoma (AML) is a benign tumor characterized by the presence of mature or immature fat tissue, thick-walled blood vessels, and smooth muscles. An AML usually occurs in the kidney as an isolated phenomenon or as part of the syndromes associated with tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM). Angiomyolipomas of the mediastinum are extremely rare.

Case Report

A 23 year old lady, with no previous known comorbidities presented with complaints of dry cough for 3 months, progressive dyspnoea on exertion for 1 month along with loss of appetite and loss of weight. There was no history of fever, chest pain, purulent expectoration, hemoptysis, ATT intake or recent TB contact.

On examination she was tachypnoic and respiratory system examination revealed left sided massive pleural effusion. All other systems were normal. Her Complete Blood Count, Renal and Liver function parameters were within normal limits.

Chest X-ray showed massive left sided pleural effusion with tracheomediastinal shift to right side. (figure 1). About 1.5 L of straw coloured pleural fluid was aspirated and the studies showed exudative neutrophilic effusion with normal glucose and low ADA (5U/L).Pleural fluid cytology was negative for malignant cells. Pleural fluid culture and sensitivity and AFB smear was negative.(Figure 2)

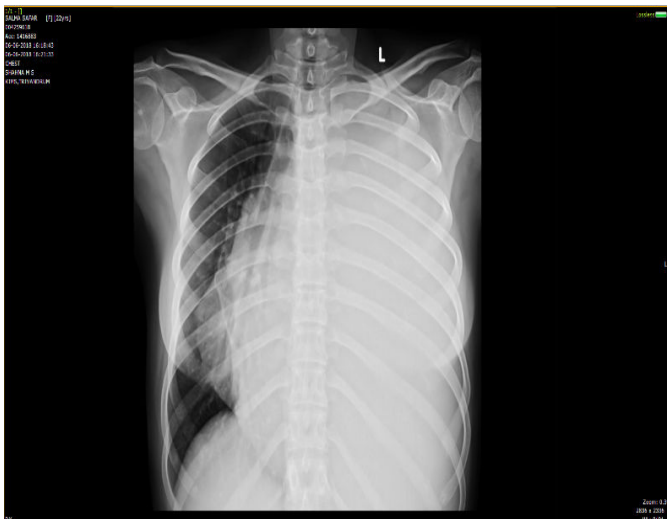

Figure 1 : Left sided massive pleural effusion

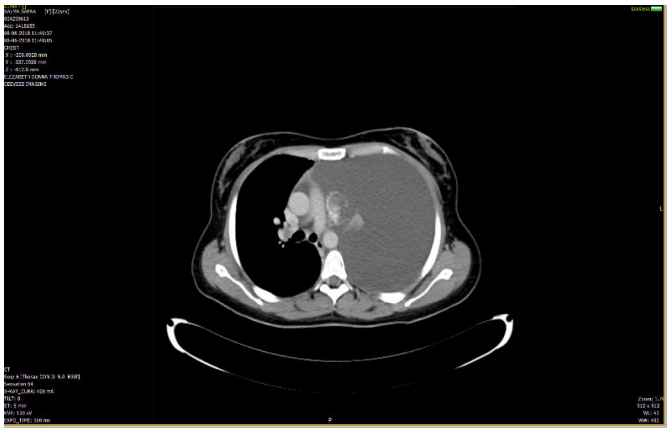

Figure 2 : CT Thorax –mediastinal window showing Left sided effusion and nderlying mass

She underwent pleuroscopy on left side which showed light pink coloured fleshy polypoidal growth in the anterior and posterior costophrenic angle, from which punch biopsy was taken. Biopsy report came as mild neutrophilic infiltration with no granuloma or atypical cells. Post procedure she continued to have large quantity of ICD drain. Repeat chest X ray after drainage of pleural fluid showed suspicious homogenous opacity in the left hilum.

We proceeded with a CECT thorax which showed relatively well defined hypodense lesion 3.2 x 3.5 cm in anterior mediastinum on left side abutting aortic arch reaching upto main pulmonary artery. It showed heterogeneous contrast enhancement with non-enhancement in periphery and fat plane with vessels was well maintained. Lung parenchyma was normal. (Figure 3, 4)

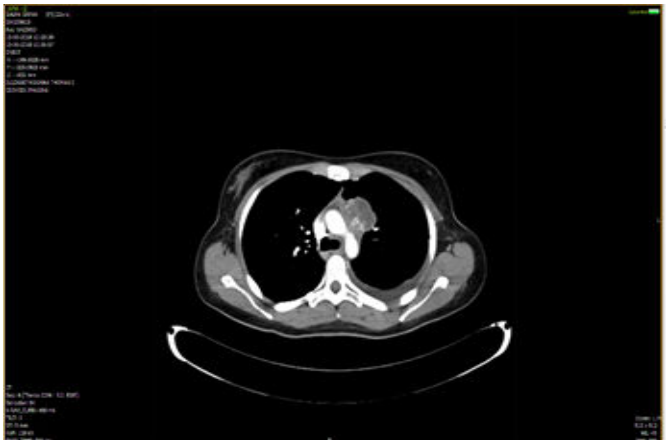

Figure 3 : CT thorax post Pleuroscopy .well defined heterogeneously enhancing mass lesion in the anterior mediastinum abutting the aortic arch

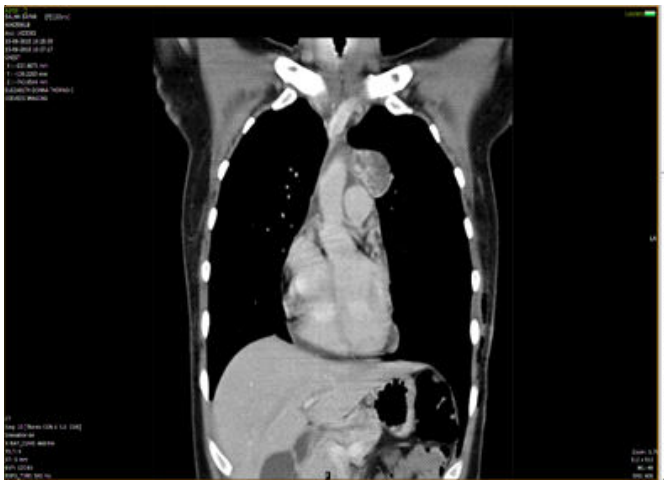

Figure 4 : CT thorax – Sagittal viewpost Pleuroscopy .well defined heterogeneously enhancing mass lesion in the anterior mediastinum abutting the aortic arch

She was referred to Cardiothoracic Surgeon. VATS excision of the mediastinal tumour & surgical pleurodesis was done. A cystic mass encapsulated with multiple lobulations seen at aortopulmonary window was completely excised and sent for histopathological examination and was reported as mediastinal angiolipoma.(figure 5,6)

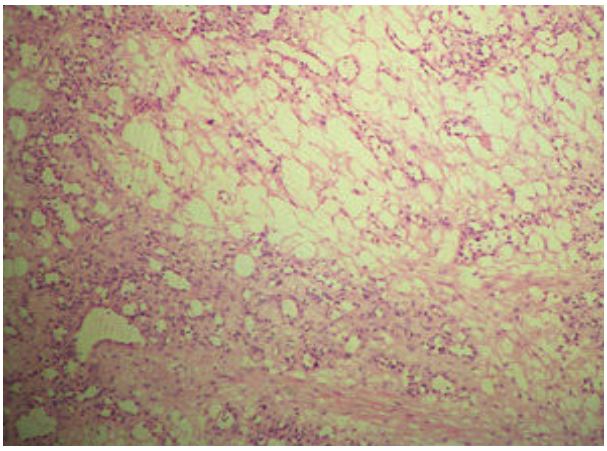

Figure 5 : Histopathology – Low power Field – Mediastinal Angiolipoma

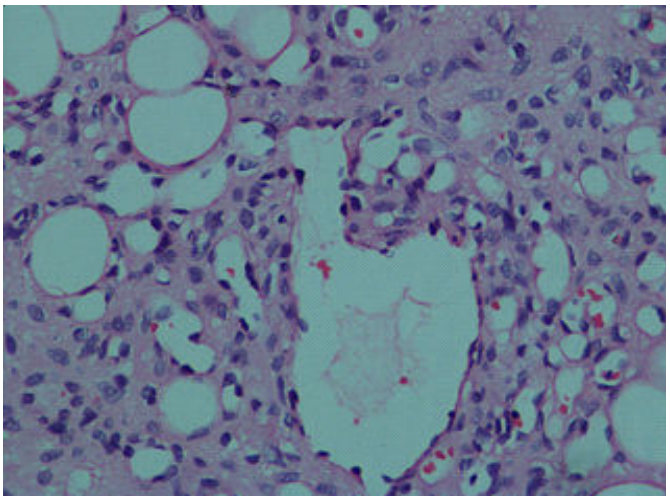

Figure 6 : High Power Field – showing adipocytes and blood vessels

On follow up she was symptomatically better with no further re-accumulation of the pleural fluid. (Figure 7.8)

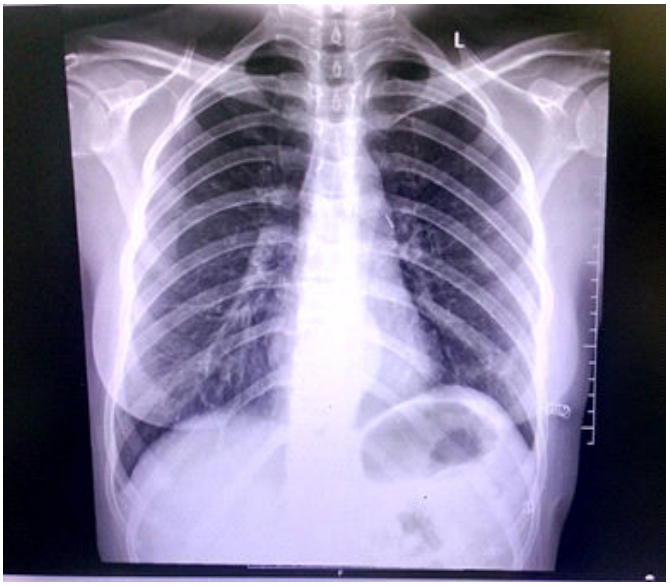

Figure 7 : Post VATS biopsy first follow up chest radiograph

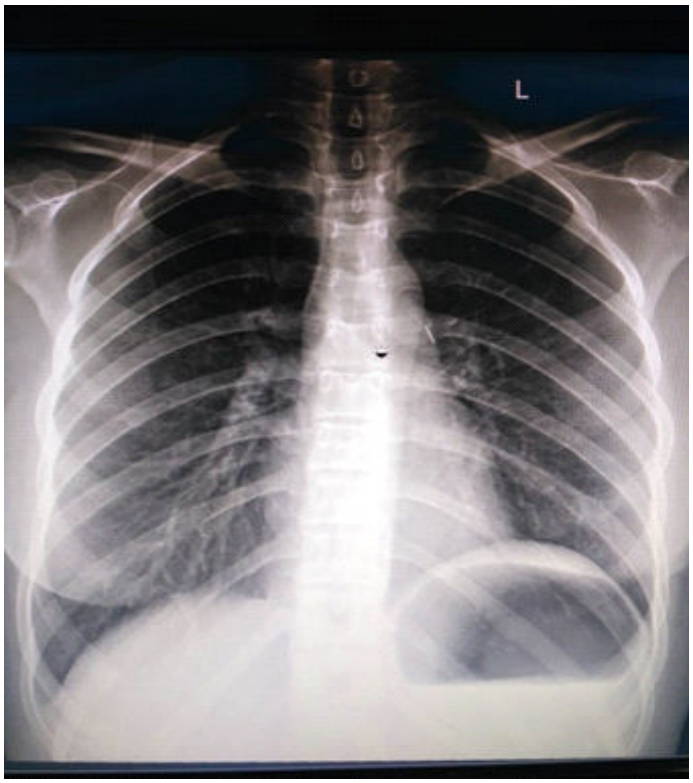

Figure 8 : Chest Radiograph – after 2 months .

Discussion

Angiomyolipomas (AML) are benign mesenchymal tumors composed of an admixture of fat, smooth muscle, and abnormal blood vessels, and the ratio of these components varies among individual patients . In our case, the smooth muscle component was absent. AMLs are usually found in the kidney. Extra renal manifestation of AMLs is uncommon but has been reported in the skin, oropharynx, abdominal wall, gastrointestinal tract, heart, lung, liver, uterus, penis, and spinal cord. The most frequently reported extra renal location is the liver. However, mediastinal manifestation of an AML is extremely rare.[1] An AML usually occurs in the kidney as an isolated phenomenon or as part of the syndromes associated with tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM)[2] . The age of onset in the previously reported cases ranged from 22 to 63 years (mean 45.6 years), with an equal sex distribution .[1] The tumors were incidentally found in some patients. Others presented with dyspnea, chest pain, dry cough, and palpitation.[1]

Previously reported treatment options for mediastinal AMLs include surgical removal and trans arterial embolization[3,4] .Trans arterial embolization has recently emerged as a first-line management option for AMLs, especially in patients with acute haemorrhage and refractory hemodynamic instability.[5]

AML of the mediastinum is a recently recognized variant with malignant potential. In addition, no long term follow-up data are available for mediastinal AMLs. Thus, complete resection of mediastinal AMLs eliminates the small possibility of malignant transformation.[6, 7]

Conclusion

Patients with AMLs should be carefully evaluated for common manifestations such as renal AMLs, Tuberous sclerosis & LAM. VATS resection of mediastinal AMLs appears to be safe and effective. Being a rare disease and responding very well to thoracoscopic resection, we are reporting this patient.

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Case report

Deciphering the forgotten clue

Anish A,[1] Sajitha M,[2] Rekha P,[3] Venugopal KP,[4] Kiran VN[5]

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ABSTRACT:

We describe a 71-year-old man who was referred to our department as bronchogenic carcinoma. He had recurrent episodes of hemoptysis, cough and pleuritic chest pain. A suspicion of an obstructive consolidation on CT thorax was confirmed on bronchoscopy. Further querying revealed history of witnessed aspiration recalled by his wife. After undergoing lobectomy the specimen showed thoracic actinomycosis, and the patient is better on antibiotics.

Key words: Thoracic actinomycosis

The Case

A 71-year-old gentleman, who runs a catering service, a known diabetic for 10 years, on oral hypoglycaemics, was referred to us with a diagnosis of Bronchogenic Carcinoma. He had a history of recurrent episodes of haemoptysis, cough and right sided pleuritic chest pain over the past 3 years. He was a reformed smoker and an occasional alcoholic. Examination showed poor oral hygiene with multiple dental caries, clubbing and respiratory examination showed features s/o right lower lobe mass/obstructive pneumonia. No supraclavicular lymphadenopathy or organomegaly was seen. Initial blood reports revealed normal total and differential blood count. Renal as well as liver functions were normal. He had uncontrolled diabetes mellitus and was therefore initiated on insulin. A Chest radiograph – posteroanterior projection (Fig 1) showed a right lower zone mass lesion. Contrast enhanced CT thorax (Fig 2) showed a heterogeneously enhancing mass lesion with air bronchograms, cavitation and low attenuation areas in the right lower lobe. His sputum (>25 pus cells with <10 epithelial cells) was negative for AFB, gram stain did not show any patho-

genic organisms, fungal elements were negative and CB-NAAT did not detect any tuberculous bacilli. Sputum culture grew only pharyngeal flora. Subsequently the possibility of a post obstructive consolidation with breaking down areas, probably due to a proximal endobronchial growth was considered. Querying him for a foreign body aspiration history in view of his alcohol consumption was unrevealing. But his wife recalled a significant aspiration of food following an alcoholic bout years back. Fiberoptic bronchoscopy (Fig 3) showed a hard intraluminal structure in the right lower lobe bronchus which was difficult to retrieve with the biopsy forceps. He already had a CECT Thorax and a PET CT done. The biopsy of the intraluminal structure turned out to be vegetable material, foreign body granuloma with numerous bacterial colonies. We proceeded to do a right lower lobectomy in view of the underlying destroyed lung and a rare possibility of underlying malignancy. The right lower lobectomy specimen showed a suppurative lung abscess with actinomycotic colonies (Fig 4)

He was managed with high dose injectable crystalline penicillin for 4 weeks and was discharged on oral Amoxicillin. He continues to be on our clinical follow up and is doing well.

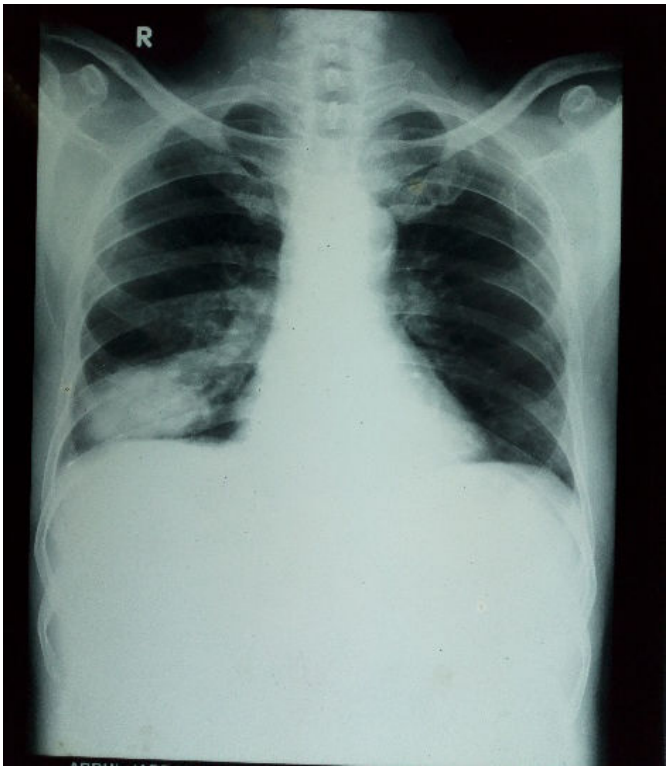

Figure 1 Chest X-ray PA showing Right Lower zone mass

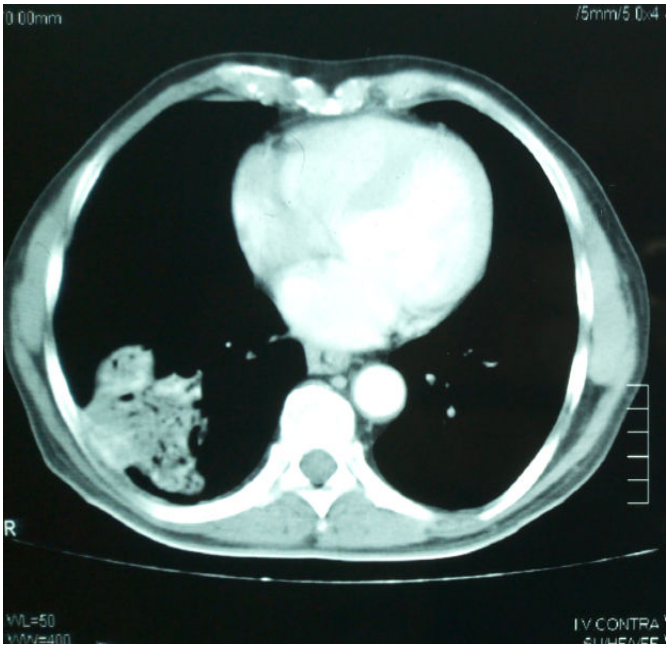

Figure 2 CECT Thorax with lung window showing consolidation with necrosis and breaking down.

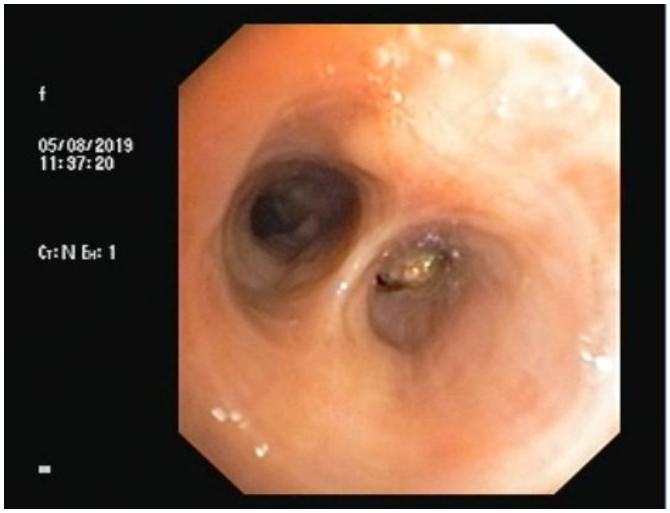

Fig 3 Fiberoptic bronchoscopy showing Intraluminal lesion right lower lobe segment

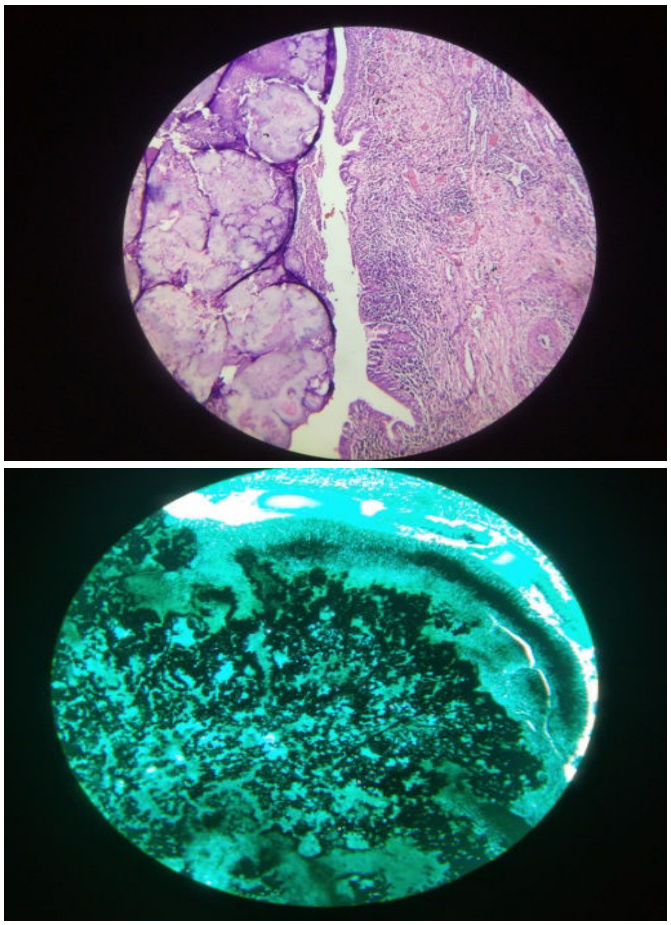

Fig 4 showing H&E, GMS staining of lung tissue with actinomycotic colonies and suppurative abscess.

DISCUSSION:

Actinomycosis, a rare invasive infection caused by *Actinomyces* species and has been described as "the most misdiagnosed disease".[1] The 3 most common sites of *Actinomyces* infection are in order of frequency, cervicofacial, abdominopelvic, and thoracic regions, although infection may involve any organ in the body. Actinomycosis typically follows a breach in the local cutaneous or mucosal barrier, such as after a traumatic injury or surgery. Involvement of the thoracic region has been postulated to present after an aspiration event in patients with poor dentition or a recent dental procedure or after aspiration of a foreign body. Notably, more than one third of patients do not have an identifiable antecedent event that would explain the onset of actinomycosis. A meticulous prodding of the history with generous time to recall events will help in narrowing the differential diagnosis as seen in our case.

Four different presentations of Thoracic actinomycosis are described which include[2]

- A Lung parenchymal form which is the most common.
- Bronchiectatic form - in which a damaged portion of lung due to prior Tuberculosis or a bacterial infection is secondarily infected with Actinomyces.

- Endobronchial Actinomycosis with broncholithiasis/ Foreign body
- Mediastinal or chest wall type

Our case fits into the endobronchial variety. Definitive diagnosis is made on bacterial culture and (especially) histopathologic examination of exudate or tissue specimen; positive culture result confirms, but negative culture result does not exclude the disease. In approximately 50% of cases, culture remains sterile[3] .It would be wise to consult with a microbiologist if actinomycosis is suspected to ensure appropriate collection, processing, and incubation. Appropriate specimens for all tests include pus from draining sinuses or abscess or tissue obtained at biopsy .Strict anaerobic processing and growth conditions are required. Presence of sulfur granules in pus from an abscess, in exudates from a sinus tract, or in a tissue specimen is highly suggestive of actinomycosis. On macroscopic appearance, the sulfur granules are typically yellow, accounting for their name, but may be white, gray, or brown. These granules microscopically can appear on hematoxylin-eosin(H&E) or Gomori methenamine silver (GMS) stains as a mass of gram-positive branching filamentous rods surrounded by the host immune response inclusive of polymorphonuclear neutrophils and a milieu of eosinophilic staining inert material often referred to as the Splendore-Hoeppli phenomenon .[4] Isolation of *Actinomyces* species on bacterial culture of a specimen obtained from a sterile site confirms diagnosis of actinomycosis; however, this may be challenging, owing to previous antibiotic therapy, inadequate culture conditions, inadequate duration of incubation, or presence of other microorganisms that inhibit growth .[5] Histopathologic examination of tissue obtained by percutaneous or surgical biopsy of the mass is the most reliable means of diagnosis. It is more sensitive than culture; demonstrates characteristic chronic granulomatous reaction, sulfur granules, and gram-positive filamentous rods.

Imaging (e.g., Ultrasound, CT, MRI) is used to identify masses or abscesses and to evaluate extent of disease in any anatomic location (e.g., thorax, abdomen, pelvis, bones, central nervous system); however, imaging findings are generally nonspecific. It may demonstrate characteristic infiltration across bony and soft tissue planes. Pulmonary actinomycosis most commonly presents as the parenchymal form with a non-segmental consolidation in the lower lobes not respecting the fissural boundaries[6,7] A clue to actinomycosis may be the presence of low attenuation areas within the consolidation or mass and adjacent pleural thickening. They may also present with pleural effusions. Acti-

nomycosis additionally can present as mass like lesions which invade and extend through chest wall or present like an empyema necessitans.[8,9]

Treatment consists of long-term therapy with beta-lactam antibiotics, Penicillin being the drug of choice. Source control, i.e. surgery to drain and remove abscess and/or infected tissue is usually reserved for cases in which antibiotic therapy alone is insufficient. It is necessary to treat the disease with high dose penicillin and for a prolonged time. Although therapy needs to be tailored to a patient's disease, penicillin intravenously 12–24 MU/day in divided doses or Injection CP 20-40 Lac units given every 4 hours for 4–6 weeks followed by oral therapy with penicillin V (1– 2g/day in divided doses every 6 hours) or Amoxicillin (1.5-3 g/day in divided doses every 8 hours for as long as 6–12 months) is a reasonable clinical approach.[10] Injection Ceftriaxone 2 gram IV 12 hourly is a reasonable alternative and will be easier to administer[11] In penicillin-allergic patients, erythromycin, doxycycline, and clindamycin are alternative agents. Imipenem and ciprofloxacin have also been reported to be effective, but there is limited clinical experience with these agents compared with the decades of data accumulated for penicillin therapy.
Metronidazole, trimethoprim-sulfamethoxazole ,ceftazidime, aminoglycosides, and oxacillin are not active against the bacteria; their use as additional agents that cover other aerobes and anaerobes in mixed infections (e.g., metronidazole) should be directed by aerobic and anaerobic cultures of adequate fluid or tissue samples harvested from the infection. Though long treatment duration of 6-12 months is advised depending on the severity of illness and extent of disease, a recent study shows that a short treatment is also effective.[12]

Summary

This case is being reported because of the rarity of the condition and this being a mimicker of malignancy and tuberculosis. The utility of tissue diagnosis cannot be over emphasized. Actinomycosis may be kept in mind as a distinctly rare differential diagnosis especially in alcoholic patients with an obstructive consolidation.

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