SELF ASSESSMENT ANSWERS

Bullous lungs: diverse aetiology

Q1: There was extensive cystic bullous involvement of lungs in both the cases, what could be the possible diagnosis?

In the first case a diagnosis of cutis laxa—that is, Ehlers-Danlos syndrome—was made in view of elastic skin, past history of being operated for bilateral inguinal hernia, aphakic eyes, and presence of mitral valve prolapse. In the second case the diagnosis of Marfan's syndrome was made in view of cardiac and skeletal abnormalities.

Discussion

The differential diagnoses of cystic bullous disease of the lungs to be considered are[1]:

- α_1-Antitrypsin deficiency.
- α_1-Antichymotrypsin deficiency.
- Cutis laxa syndromes.
- Sallas disease.

Other acquired causes are:

- Inorganic dust exposure and cadmium exposure.
- Injected dissolved methyl phenidate tablets.
- Idiopathic non-arteriosclerosis cerebral calcification syndrome.

Ehlers-Danlos syndrome is a hereditary disease of connective tissue and sufferers were classically known as "India rubber men". In this syndrome there are nine subtypes, type-1–9 varying in severity from the severe form with bilateral joint hypermobility and velvety hyperextensible skin to milder forms. Other associated abnormalities are inguinal and diaphragmatic hernias, ectasia of portions of the alimentary tract, large arterial rupture, varicose veins, mitral valve prolapse and various eye changes.[2] Thoracic abnormalities reported in Ehlers-Danlos syndrome include recurrent sinusitis and pneumonia, unexplained haemoptysis, panacinar emphysema with bullae, tracheobronchomegaly and recurrent pneumothorax, pectus excavatum, straight back syndrome, and raised gas transfer factor on lung function testing.[3]

The diagnosis of Marfan's syndrome is made by the presence of two major criteria, each from different body system, and involvement of at least one other system. The major criteria are ectopia lentis, aortic dilatation/dissection, dural ectasia,[4] presence of four out of eight skeletal manifestation, and a positive family/genetic history. Minor criteria include joint hypermobility, high arched palate, scoliosis, and pectus deformity.

Pulmonary manifestations are observed in 10% of cases of Marfan's syndrome which are generalised honey combing, spontaneous recurrent pneumothorax, bronchiectasis, bullae, upper lobe fibrosis, ciliary dyskinesis, deformities of the thoracic cage, tracheal weakness, decreased total lung capacity, decreased vital capacity, decreased diffusion lung capacity for carbon monoxide, decreased elastic lung recoil, and obstructive sleep apnoea syndrome.[5–7] Our patient was being wrongly treated with antituberculosis treatment in the past for upper lobe fibrosis.

In conclusion, in patients with bullous lung disease a systemic aetiology should always be ruled out.

Final diagnosis

Case 1: Ehlers-Danlos syndrome; case 2: Marfan's syndrome.

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Learning points

- Ehlers-Danlos and Marfan's syndromes should be suspected in patients with excessive skin and joint hyperextensibility.
- Connective tissue disorders may be present for many years before lung manifestation may occur.
- Thoracic abnormalities in Ehlers-Danlos syndrome include recurrent sinusitis and pneumonia panacinar emphysema with bullae, tracheobronchomegaly and recurrent pneumothorax, pectus excavatum, straight back syndrome.
- Marfan's syndrome should be considered in the differential diagnosis of upper lobe fibrosis.

Persistent dizziness

Q1: What are the two significant electrocardiographic findings in this clinical context?

Intermittent sinus rhythm and intermittent ventricular paced beats with retrograde ventriculoatrial conduction (QRS complexes 1, 2, 8, and 9 in the rhythm strip).

Q2: What is the diagnosis?

Pacemaker syndrome.

Q3: What is the definitive treatment?

Dual chamber pacemaker with mode switching.

Discussion

During the initial presentation, the 24 hour Holter revealed atrial fibrillation with pauses of 6 seconds. Hence a VVIR pacemaker was inserted. However subsequent 24 hour Holter revealed intermittent sinus beats as well as paced beats with ventriculoatrial retrograde conduction; these are two of the key factors that could cause the pacemaker syndrome. The initial 24 hour tape picked up only atrial fibrillation and intermittent sinus rhythm could have developed subsequently. Ventriculoatrial retrograde conduction explained in detail later is a particular problem when patients are paced for atrial fibrillation with prolonged pauses rather than for complete heart block.

Box 1: Main risk factors for development of pacemaker syndrome

- Elderly.
- Single chamber ventricular pacemaker (VVI/VVIR).
- Sinus rhythm.
- Retrograde ventriculoatrial conduction.
- Associated left ventricular disease.

Before proceeding with the discussion of pacemaker syndrome, brief review of pacemaker terminology is not inappropriate. Pacemakers are described by using three to five letters. The first letter describes which heart chamber or chambers paced: A for atrium, V for ventricle, or D for dual (both the atrium and the ventricle). The second letter refers to the chamber in which the pacemaker is able to sense intrinsic cardiac events: A for atrium, V for ventricle, or D for dual. The third letter indicates the pacemaker's mode of response to intrinsic cardiac events: I for inhibit, T for trigger, and D for dual. Inhibition means the pacemaker will not pace after it senses intrinsic depolarisation. Triggered applies to dual chamber pacemakers and single chamber ventricular pacemakers that can sense the atrium (for example, VDT). When an intrinsic atrial depolarisation is sensed, ventricular pacing is triggered. D as a third letter means that the pacemaker is capable of both being inhibited and triggered by intrinsic cardiac events. R as a fourth letter indicates rate modulation, which allows the pacemaker to pace above its programmed upper limit in response to exercise. Antitachycardia functions may be represented in the fifth letter.

Pacemaker syndrome was first described in 1969 by Mitsui *et al* and he also linked it to the atrioventricular dysynchrony caused by single chamber ventricular pacing.[1] However it can also be associated with dual chamber pacing, usually as a result of suboptimal atrioventricular synchrony or rapid atrial or ventricular pacing.[2]

The reported prevalence of pacemaker syndrome varies widely (20%–83%), perhaps because no standardised system exists for diagnosis of the syndrome.[3 4]

The prevalence of pacemaker syndrome may be underestimated for two reasons. Firstly, the syndrome is mistaken for worsening heart failure or coronary heart disease. Secondly, often the pacemaker recipient who experienced syncope before pacemaker implantation may not report the less troublesome signs and symptoms of pacemaker syndrome to their healthcare providers.[5]

The risk factors for developing pacemaker syndrome are listed in the box 1.

Atrioventricular dysynchronous pacing such as VVI/VVIR modes results in loss of atrial contribution to ventricular filling and the cardiac output may go down up to 35%, especially in diseased ventricles.

Box 2: Key signs and symptoms of pacemaker syndrome

- Dyspnoea.
- Fatigue.
- Dizziness/presyncope/syncope.
- Palpitations.
- Chest pain.
- Confusion.
- Cannon waves.

Another factor that contributes to pacemaker syndrome is retrograde conduction (from ventricle to atria). It occurs in some patients who receive single chamber ventricular pacemakers. Because the lead of a ventricular pacemaker is positioned in the apex of the right ventricle, paced depolarisation of the ventricles proceeds in a cell-to-cell fashion from the right ventricular apex to the entire right and left ventricles. It can then continue to the atria, causing atrial depolarisation. This process is termed retrograde depolarisation of the atria. As 90% of retrograde conduction occurs through the atrioventricular node, the potential for retrograde conduction is preserved unless the atrioventricular node is diseased.[6] It causes atrial contraction against closed atrioventricular valves thus increasing atrial and pulmonary venous pressures. This activates systemic vasodepressor reflexes, which are mediated by vagal stimulation, sympathetic inhibition, or release of atrial natriuretic peptide thereby resulting in hypotension.

Though pacemaker syndrome may very rarely occur with atrial pacing as well as dual chamber pacing, it is very much less common in these modes when compared with VVIR mode. With atrium paced, atrium sensed, inhibitory pacing (AAI), atrioventricular dyssynchrony may result from very long PR intervals, particularly at faster paced beats, during rate responsive (AAIR) pacing. Atrioventricular dysynchrony can also occur in dual chamber pacing with non-atrial tracking pacing modes, long programmed atrioventricular delays, loss of atrial capture as well as during pacemaker-mediated tachycardia. Prolonged intra-atrial conduction times can lead to simultaneous atrial and ventricular activation thereby resulting in the pacemaker syndrome in dual chamber paced, dual chamber sensed, dual response to sensing (triggered and inhibitory) (DDD) pacing.

The key signs and symptoms of pacemaker syndrome are listed in the box 2.

The diagnosis requires clinical correlation with 24 hour Holter monitoring/event recorder.

In patients with paroxysmal atrial fibrillation as in this patient, the treatment of choice is the upgrading of pacemaker to a dual chamber device with mode switching.

Pacemakers with mode switching function can sense the conversion from a sinus rhythm to atrial fibrillation or atrial flutter and automatically switch from DDD mode to VVI pacing to prevent rapid ventricular pacing. When the patient flips to sinus rhythm, mode switch reprograms the pacemaker to DDD thereby maintaining atrioventricular synchrony. Normally, mode switch will not cause pacemaker syndrome; however, inappropriate mode switching in response to muscle artifact rather than rhythm change can result in pacemaker syndrome.

Allowing sinus rhythm preference by decreasing the lower pacemaker rate in VVI pacing can also be useful. However it often requires upgrading to dual chamber pacemaker. In one study, 26% of patients who received single chamber ventricular pacemakers experienced pacemaker syndrome, which required upgrading to dual chamber devices.[7] Pacemaker upgrade is a more complex procedure than initial system implantation. Though it is usually possible to upgrade the pacemaker, it takes longer and there is a higher incidence of complications, particularly atrial lead displacement when compared with initial system implantation.

Learning points

- Pacemaker syndrome mainly occurs in VVI pacing due to loss of atrioventricular synchrony.
- Low cardiac output symptoms in the presence of VVI pacing should prompt investigations.
- The optimum mode of pacing in patients with paroxysmal atrial fibrillation is DDD pacing with mode switch.

Final diagnosis

Pacemaker syndrome due to paroxysmal atrial fibrillation.

References

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Young man with progressive weight loss, fevers, and a hilar mass

Q1: What is the diagnosis?

Endobronchial nocardiosis.

Q2: What is the most appropriate therapy for this patient?

Trimethoprim-sulfamethoxazole.

Discussion

Nocarida was first described by the French veterinarian Edmund Nocard in 1888. Nocardia is a genus in the family nocardiaceae, and there are nine species recognised. *Nocardia asteroides* is the cause of 80%–90% of all cases of nocardiosis.[1] The organism is characteristically a beaded, Gram positive bacillus, which is weakly acid fast. Definitive diagnosis of nocardiosis requires identification of the organism in culture, as the histological appearance of the organism is not unique. Nocardia will grow in a variety of culture media but is slow growing. It is typically identified after 4–5 days but may take up to four weeks to be isolated.[1 2]

Historically, nocardia were believed to be fungi that only rarely caused disease in humans; however it has now been established that these bacteria may be relatively common pathogens and cause a variety of clinical problems in humans. The main host defence against nocardia is a cell mediated immune response, hence, patients with HIV, lymphoreticular malignancies, and solid organ transplants are at increased risk for developing nocardiosis. Other predisposing conditions include chronic lung disease, systemic lupus erythematosis, tuberculosis, diabetes mellitus, Cushing's syndrome, or alveolar proteinosis.[3] Steroids add significantly to the risk for developing nocardiosis and have been associated with up to 20% of all cases. Interestingly, 50% of cases of nocardiosis occur in patients with no underlying disease or immunosuppressive therapy.

The clinical manifestations of nocardiosis are diverse and patients may present with non-specific systemic symptoms, including anorexia, weight loss, and high fevers. Thus, nocardiosis can mimic common illnesses such as lymphoma, tuberculosis, sarcoidosis, and other granulomatous infections. Cough, when present, is typically productive of thick mucopurulent sputum. A high index of suspicion in an appropriate clinical setting is required to make the diagnosis.[2 3]

The lung appears to be the most commonly involved organ, however, disseminated infection involving the brain, muscle, bone, and skin may occur. The infection usually begins in the respiratory tract and 75% of patients exhibit a primary pneumonitis. The radiological manifestations of nocardiosis are variable, including lobar infiltrates or consolidation, thick walled cavities, or solitary nodules. Miliary lesions, adult respiratory distress syndrome, and pleural effusions have also been noted.[3 4] When effusions are present, they are almost always associated with parenchymal infiltrates. The fluid can be either serous or purulent and is always exudative as in our patient. Uncommonly, nocardiosis may present as an endobronchial mass lesion as in this case.[5–7] The radiological features of mass lesion has a broad differential including a variety of infections such as actinomycosis, fungal infections such as blastomycosis and coccidiodomycosis in endemic areas, bacterial infections such as *Staphylococcus aureus*, malignancies such as primary bronchial carcinomas and lymphomas.[5] In the case described the short history and a productive cough were more suggestive of an infection than a malignancy. Gram staining of the bronchial wash

Learning points

- Impaired cell mediated immunity predisposes patients to develop nocardiosis, however it may occur in apparently normal hosts as in the case described.
- The clinical manifestations of nocardiosis are diverse. Pulmonary nocardiosis may rarely produce an endobronchial mass lesion and radiological features that can mimic malignancy.