ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 1, 2016

ISSN - 0974-2441

Case Report

PENICILLAMINE IN INTERSTITIAL LUNG DISEASE: A TIMELY REMAINDER OF AN OLD FOE

PAWADSHETTAR S, ACHARYA VK, ARUN M, UNNIKRISHNAN B, TANTRY BV

Email: achvish@gmail.com

Received: 10 November 2015, Revised and Accepted: 31 November 2015

ABSTRACT

Penicillamine-induced lung injury has been sparsely reported in the literature. We report one such case with its wide-ranging ramifications. We present an unusual case of drug induced-interstitial lung disease (DI-ILD) caused by penicillamine, resulting in acute lung injury in a young patient with Wilson's liver disease. Patient had a interstial lung disease which was attributed to the drug pencillamine. Penicillamine-induced lung injury has been sparsely reported in the literature and dose-dependent toxicity in a patient with neuro-psychiatric diseases adds to the rarity of the case. Furthermore, the complexities involved in diagnosing DI-ILD are deliberated.

Keywords: Interstitial lung disease, Wilson's disease, Penicillamine.

INTRODUCTION

Drug-induced (DI) lung disease is a major source of iatrogenic injury. Awareness of DI pulmonary disease is increasing. A review published in 1972 identified only 19 drugs as having the potential to cause pulmonary disease [1]; now at least 150 agents are recognized [2,3] and the list continues to grow. Adverse reactions occur in about 5% of patients receiving any drug, and 0.03% of hospital deaths are believed to be drug-related [2]. But this could be grossly under-reported as DI lung injury and deaths are difficult to diagnose and are often diagnosed only by exclusion.

In this article, we present a rare case of penicillamine causing acute lung injury and interstitial fibrosis which was dose-dependent. Though penicillamine has been known to cause interstitial lung disease (ILD) very few reports and limited clinical evidence establishes the novelty of our case.

CASE REPORT

A 36-year-old male presented with complaints of tremors involving left upper limb followed by left lower limb and slurred speech since 1½ years with worsening of symptoms since 1½ weeks. History of mood disorder including depression was present.

The patient was previously evaluated with magnetic resonance imaging which was suggestive of predominant cerebellar degeneration. Patient's liver function tests revealed low serum ceruloplasmin levels of 5.66 mcg/dl (normal 20-60 mcg/dl), low serum copper levels of 34 mcg/dl (normal 70-140 mcg/dl), a high 24 hrs urinary copper levels of 856 mcg (normal 12-60 mcg). Slit lamp examination revealed Kayser-Fleischer rings. Based on the above consistent clinical and laboratory features a diagnosis of Wilsons disease made, and the patient was started on D-Penicillamine 500 mg thrice a day and Zinc 200 mg thrice a day.

1 week later patient developed low-grade fever, severe dry cough, breathlessness and diffuse erythematous maculopapular rash all over the body. Patient did not improve on symptomatic treatment. Breathlessness progressed from Grade I to Grade III Modified Medical Research Committee grade.

General examination showed the presence of tachypnea, with saturation of 80% on room air. Respiratory examination revealed bilateral diffuse crepitation.

Patients' blood counts including erythrocyte sedimentation rate were normal. Blood and sputum culture showed no growth.

A portable plain radiograph revealed bilateral reticular opacity. In view of skin rash, acute onset of breathlessness and infective causes were ruled out, drug toxicity was considered. A high-resolution computerized tomography (HRCT) along with expiratory scans was done (Figs. 1-3). A pulmonary function test was performed once patient stabilized and it showed moderate restrictive lung pattern.

In the background of recent initiation of specific drug therapy for proven liver disease the etiology was attributed to D-Penicillamine. The offending drug was stopped immediately, and patient was started on inhaled corticosteroids, N-acetyl cysteine 600 mg thrice a day and parenteral methyl prednisolone 60 mg thrice a day for a week with other symptomatic measures. Patient improved substantially with the treatment and symptoms subsided. A repeat chest plain radiograph was normal.

DISCUSSION

Drugs as etiological agents of ILD are confounding for two main reasons: One is that they offer a coherent explanation to a sizeable number of ILD cases seen in clinical practice [4]; and the second is that early withdrawal of the causative drug will often lead to improvement or even cure of the ILD.

DI lung injury has various patterns of pathogenesis in the presentation. The recognized ones are,

- Hypersensitivity reactions
- Non-cardiogenic pulmonary edema
- Interstitial pneumonitis
- Pleural and mediastinal disorders
- Pulmonary vascular disease
- DI Lupus
- DI bronchospasm

John Walshe first described the use of penicillamine in Wilson's disease in 1956 [5]. He had discovered the compound in the urine of patients (including his own) who had taken penicillin, and experimentally confirmed that it increased urinary copper excretion by chelation.

Penicillamine is a drug of the chelator class. It is an alpha amino acid metabolite of penicillin although it has no antibiotic properties. Penicillamine is used as a form of immunosuppression to treat rheumatoid arthritis [6]. It works by reducing numbers of T-lymphocytes, inhibiting macrophage function, decreasing IL-1, decreasing rheumatoid factor, and preventing collagen from cross-linking. Other uses include in Rheumatoid arthritis, Lead poisoning, cystinuria.

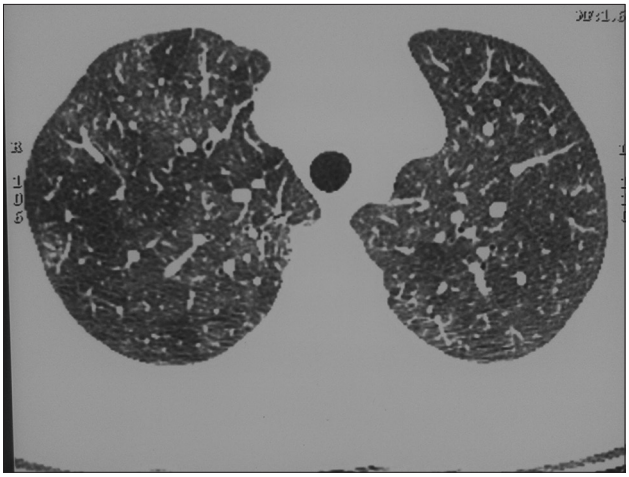

Fig. 1: High resolution computerized tomography chest shows alternate areas of hyper and hypoattenuation suggestive of mosaic pattern

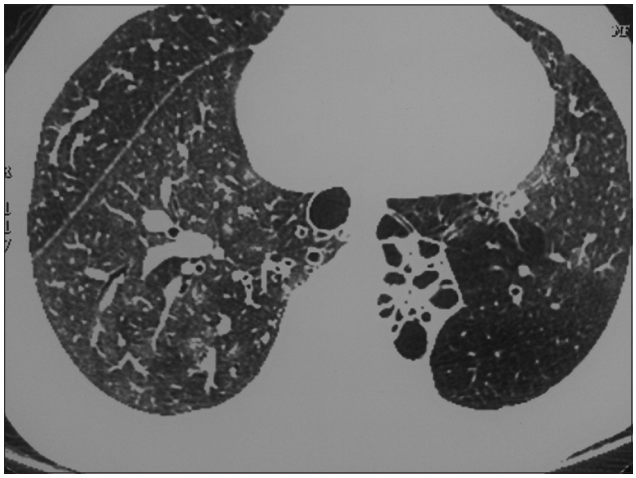

Fig. 2: High resolution computerized tomography chest shows areas of air trapping in expiratory scans suggestive small airway involvement

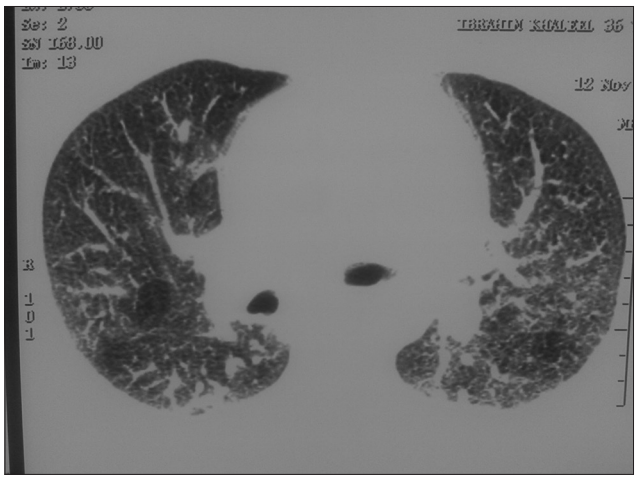

Fig. 3: High resolution computerized tomography chest peribronchovascular interstitial thickening in the upper lobes

In Wilson's disease a dose of 500-1500 mg is indicated for initiation and titrated to achieve urinary copper levels of 0.5-1 mg per day. In our patient owing to psychiatric manifestations of the disease a higher dose was consumed by the patient inadvertently, which resulted in dose-dependent toxicity.

Adverse effects from drugs on the respiratory system have emerged as a significant topic in pulmonology and represent a sizeable proportion of patients seen in pulmonary practice in recent times. Under the impetus of a French study group on DI respiratory disease, known as the Grouped' Etudes de la Pathologie Pulmonaire Iatrogène, a comprehensive table of drugs initiating adverse respiratory reactions has been drawn up [7].

It is difficult to estimate the exact frequency of DI-ILD (DI-ILD) for several reasons, including the following: (1) The use of plain chest radiography is likely to underestimate subclinical forms of DI-ILD, compared with HRCT [8]. (2) Many drugs that induce ILD are used primarily by non-respiratory physicians, and under diagnosis is possible. (3) In oncology patients, where DI-ILD is common, and the differential diagnosis is broad, the ultimate diagnosis will often remain presumptive because the severe clinical status of the patient precludes the use of invasive diagnostic techniques. (4) Another possible reason is, some of the diseases like rheumatoid arthritis in which penicillamine is used can induce ILD and superimposed drug-induced ILD may be under reported or undiagnosed.

A major, but largely unresolved question is why, out of the treated population of patients, only some individuals will develop DI-ILD. A limiting dose has only been identified for a few drugs [9]. For most drugs, there is no apparent role of dosage or duration of treatment in relation to the likelihood of developing adverse effects, i.e., development remains largely unexpected and idiosyncratic.

Various histological patterns are recognized. Apart from conventional patterns of ILD as non-specific interstitial pneumonia (cellular or fibrotic), eosinophilic pneumonia [10], or pulmonary fibrosis, drugs can also elicit less usual patterns such as organizing pneumonia (OP, previously designated BOOP), or desquamative interstitial pneumonia [11].

Penicillamine has been attributed to cause few recognized patterns including acute and sub-acute pneumonitis, eosinophilic pneumonia, organizing pneumonia Adult Respiratory Distress Syndrome, diffuse alveolar hemorrhages and Goodpasture's disease. A case of Goodpasture's disease was reported in a patient with Wilsons Disease [12].

The primary goal of treatment in DI-ILD is to suppress the inflammatory response and prevent the deposition of fibrotic tissue. Treatment consists mainly of discontinuing the offending drug immediately, and supportive management of the pulmonary symptoms, e.g., inhaler therapy and oxygen if required until the drug-induced lung disease improves. Challenge tests (reintroducing the suspected medication to see if symptoms recur) are rarely performed.

Steroid therapy (such as prednisolone) is sometimes used to quickly reverse the lung inflammation caused by the offending drug [13]. Prognosis of acute drug-induced ILD is usually excellent. Symptoms will resolve within 24-48 hrs, with full recovery generally being achieved. Chronic syndromes may take longer to resolve but often leave significant scarring that may need long-term supportive therapy.

CONCLUSION

Penicillamine is not a very commonly cited drug as a cause of ILD. Since the drug is being used more widely in recent days for diverse conditions, clinicians should be aware of the possible toxic effects on the lung and also should have a high index of suspicion as drug-induced ILD is also masqueraded by the disease process and definitive diagnosis is generally not possible and is often by exclusion, by establishing a temporal relationship with the offending agent and assessing response after withdrawal of the offending drug.

REFERENCES

1. Rosenow EC. The spectrum of drug-induced pulmonary disease. Ann Intern Med 1972;77(6):977-91.
2. Fraser RS, Müller NL, Colman N, Pare PD. Pulmonary disease caused by toxins, drugs, and irradiation. Diagnosis of Diseases of the Chest. 4th ed. Philadelphia: W.B. Saunders; 1999. p. 2517-92.
3. Rosenow EC. Drug-induced pulmonary disease. Dis Mon 1994;40(5):253-10.
4. White JP, Ward MJ. Drug-induced adverse pulmonary reactions. Adverse Drug React Acute Poisoning Rev 1985;4(4):183-211.
5. Walshe JM. Wilson's disease; new oral therapy. Lancet 1956;267(6906):25-6.
6. Camp, A. Penicillamine in the treatment of rheumatoid arthritis. Proc R Soc Med 1977;70(2):67-9.
7. Foucher P, Biour M, Blayac JP, Godard P, Sgro C, Kuhn M, *et al*. Drugs which may injure the respiratory system. Eur Respir J 1997;10(2):265-79.
8. Ellis SJ, Cleverley JR, Müller NL. Drug-induced lung disease: High-resolution CT findings. Am J Roentgenol 2000;175(4):1019-24.
9. Aronin PA, Mahaley MS, Rudnick SA, Dudka L, Donohue JF, Selker RG, *et al*. Prediction of BCNU pulmonary toxicity in patients with malignant gliomas: An assessment of risk factors. N Engl J Med 1980;303(4):183-8.
10. Sitbon O, Bidel N, Dussopt C, Azarian R, Braud ML, Lebargy F, *et al*. Minocycline pneumonitis and eosinophilia: A report on 8 patients. Arch Intern Med 1994;154(14):1633-40.
11. Bone RC, Wolfe J, Sobonya RE, Kerby GR, Stechschulte D, Ruth WE, *et al*. Desquamative interstitial pneumonia following long-term nitrofurantoin therapy. Am J Med 1976;60(5):697-01.
12. Scott DL, Bradby GV, Aitman TJ, Zaphiropoulos GC, Hawkins CF. Relationship of gold and penicillamine therapy to diffuse interstitial lung disease. Ann Rheum Dis 1981;40(2):136-41.
13. Kubo K, Azuma A, Kanazawa M, Kameda H, Kusumoto M, Genma A, Saijo Y, *et al*. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respir Investig 2013;51(4):260.