Concurrent Massive Breast Enlargement, Myasthenia Gravis and Dermopathy as Manifestations of Penicillamine Toxicity in A Wilson's Disease Patient

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SUMMARY

Penicillamine toxicity in Wilson's disease has been well reported but rarely seen now as newer agents are being used. We present a case who developed multiple rare complications of Penicillamine concurrently. Our patient is one of three siblings on Penicillamine, she was the only one who developed massive breast enlargement four months after commencing Penicillamine therapy, as well as dermatological adverse reactions and myasthenia gravis three more months later. All the adverse effects improved soon after substitution of the offending agent with Trientine.

KEY WORDS:
Penicillamine toxicity, Wilson's disease, breast enlargement, dermopathy, myasthenia gravis.

INTRODUCTION

In 1956, John Walshe identified Penicillamine as a treatment for Wilson's disease (WD) because of its copper-chelating property [1]. The current guidelines recommended chelating agents, Penicillamine or Trientine in the treatment of WD with the latter considered to be better tolerated[1].

Breasts gigantism is a rare side effect. Case reports have mainly been in rheumatology patients and only occasionally in WD [2,3,4].

There are many other more common adverse effects from Penicillamine. They can be divided into three groups. The common early mucocutaneous reactions are mouth ulcers and rash. The later ones are nephrotoxicity, lupus like syndrome, bone marrow and dermatological toxicities. The very late side effects are myasthenia gravis, polymyositis and others [1,5].

We present an interesting case of WD with multiple rare adverse effects of Penicillamine. Intriguingly, she is the only one developing these complications despite having two siblings on the same medication for almost similar durations.

CASE REPORT

This 16 year old female presented to our hospital in July 2010. Ten months earlier, she was diagnosed with WD based on a low serum ceruloplasmin < 0.09 g/l and bilateral Kayser-Fleischer rings after her eldest sister was diagnosed with WD. All three siblings have WD and were treated with Penicillamine.

Our patient was the only one who developed side effects from Penicillamine. She was initially started on Penicillamine at 250 mg once daily and gradually increased to thrice daily.

Four months later, she complained of massive bilateral breasts enlargement, galactorrhoea, diplopia, jaw weakness with difficulties in smiling, chewing and talking.

Investigations revealed an elevated prolactin level of 1082 mu/l (normal 59-619 mu/l). She was not on medication known to increase prolactin levels. The thyroid function tests and follicle stimulating hormone were normal. Magnetic resonance imaging (MRI) of her brain revealed mild pituitary hyperplasia.

The MRI of breasts with dynamic contrast showed gross breast hypertrophy bilaterally, with marked glandular hyperplasia and enhancement (see figure 1). There was a dominant lobulated mass in the right breast with type 1 enhancement curve consistent with fibroadenoma or fibroadenosis (see figure 2).

She was commenced on cabergoline 0.5 mg twice a week. The breast enlargement did not improve although the galactorrhoea stopped. Her prolactin level decreased to 6.4 mu/l after 5 weeks of cabergoline and it was discontinued after 2 months.

Subsequently she was referred to us. On examination we noted hirsutism, bilateral ptosis with the right eyelid affected more than the left, dysarthria and dysphonia. She had mild proximal limbs weakness. Both her breasts were markedly enlarged and tender. The overlying skin had prominent peau d'orange and erythematous scaling patches. Other dermatological changes were hyperpigmentation on her face and forearms and atrophic scaling skin and lichenified patches on her fingers.

Repetitive nerve stimulation test showed a decremental response of the right deltoid and orbicularis muscles consistent with a neuromuscular junction disorder. The creatinine kinase 148 u/l (normal 25-170 u/l) and aspartate transaminase 28 u/l (normal ≤ 31 u/l) were normal.

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Table I: Measurements of the patient breasts at presentation, 3 and 7 months after discontinuation of Penicillamine

Measurement points	Size at presentation.	Size at 3 months after discontinuation of Penicillamine.	Size at 7 months after discontinuation of Penicillamine.
Chest diameter around the nipple area in cm.	101	98	98
Chest diameter at infra-mammary fold in cm.	75	75	77
The distant from sternal notch to the nipple in cm.	Left breast: 37 Right breast: 39	Left breast : 35 Right breast: 36	Left breast : 34 Right breast: 33.5
The distant from mid-clavicular point to the nipple in cm.	Left breast: 37 Right breast : 39	Left breast : 34 Right breast : 35	Left breast : 34 Right breast : 32

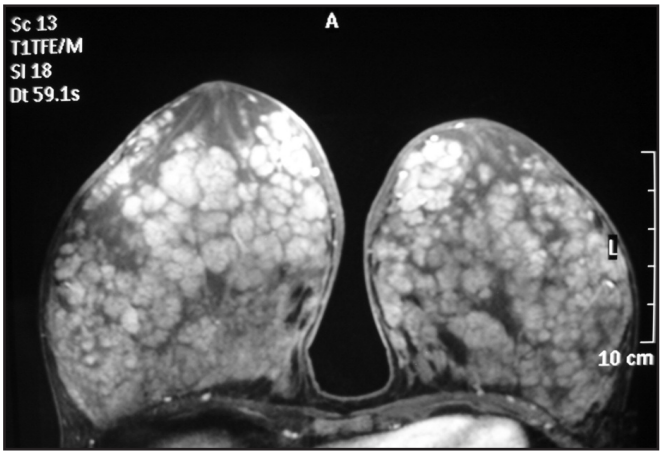

Fig. 1: MRI Of The Breasts : post contrast T1 fat saturation showing grossly enlarged breasts measuring 18 cm x 16 cm x 13 cm on the right and 15 cm x 14 cm x 14 cm on the left with marked glandular enhancement.

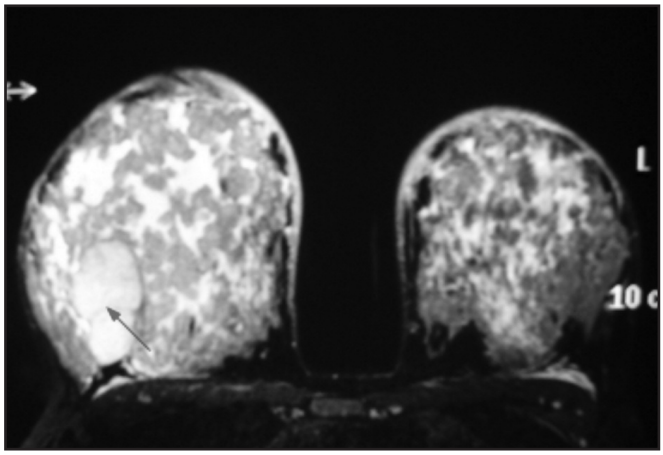

Fig. 2: MRI Of The Breasts : T2 Weighted fat saturation showing a bright lesion measuring 6 cm x 4 cm x 3.5cm in the right breast with thin septation (arrow) within. This lesion showed Type 1 kinetic enhancement curve suggestive of a fibroadenoma.

She also had detectable anti-nuclear antibody (ANA) at a titre of 1: 640, anti-topoisomerase I antibody and anti-ribonucleoprotein antibody but no features suggestive of lupus or other connective tissue diseases.

We discontinued penicillamine and commenced her on trientine 300 mg thrice daily. The dermatologist prescribed Ung Emulsifying Ointment soap and emollient thrice daily, topical clobetasone butyrate twice daily and oral hydroxyzine 25 mg thrice daily.

On follow up at one month after stopping Penicillamine, she reported disappearance of the visual and skin complaints. She also noticed less problem with chewing and the ptosis resolved.

In the subsequent follow-ups at 7 months after discontinuation of Penicillamine, she reported resolution of all the neurological and dermatological side effects. There was no recurrence of galactorrhoea and the breasts size reduced further as shown in table I. The ANA became undetectable and the prolactin level remained normal.

DISCUSSION

In this case, we attributed the massive breast enlargement, myasthenia gravis and dermopathy to Penicillamine because there is a time correlation of Penicillamine therapy and its discontinuation to their appearance and disappearance. All the three complications are known in Penicillamine therapy but infrequent therefore it should be even rarer to find them occurring in the same patient.

Breast gigantism is a distressing but fortunately rare complication of Penicillamine. The onset of breast enlargement or gigantism can begin as early as 12 weeks after initiating Penicillamine [3].

Our patient had massive breast enlargement as well as galactorrhoea and hyperprolactinemia. Penicillamine is not one of the medications known to cause hyperprolactinemia [5]. We have found one case who was on Penicillamine for a rheumatological condition with breast gigantism and galactorrhoea [3]. The galactorrheoa stopped after Penicillamine withdrawal but her breast size remained unchanged.

The histology of breast tissue obtained from reduction mammoplasty in a case revealed fibroadenoma with ductal hyperplasia [4]. The finding is consistent with the breast MRI impression of our patient.

Breast gigantism usually requires further treatment with danazol [2] or surgical reduction [4].

Ocular myasthenia gravis is another rare complication of Penicillamine which occurred in our patient. Myasthenia gravis is one of the few adverse effects of Penicillamine which is thought to be of auto-immune in origin [5].

The types of dermatological reactions to Penicillamine were pruritic maculo-papular rash, increased skin friability, excessive wrinkling of skin, pemphigus vulgaris, aphthous stomatitis and lichen planus [5]. While pruritic rash is due to allergic reaction, the other mechanisms of skin side effects are immunological or effect on collagen [5].

The pathophysiologies of the three adverse effects were not well studied. Since myasthenia gravis and some of the dermatology side-effects are immune mediated; and here together with the presence of other auto-antibodies, we hypothesize that Penicillamine induced breast enlargement may also be immune related.

In conclusion, the adverse effects of Penicillamine can occur at any time during therapy with some potentially fatal but reversible when therapy was discontinued early. And since Penicillamine is still an effective first line treatment for WD, all clinicians should be well verse with its side effects and their management.

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