

## Case Report

# Primary biliary cirrhosis in a patient with generalised morphoea

## 原發性膽汁性肝硬化伴發不定型硬皮病

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A 66-year-old Chinese man with primary biliary cirrhosis (PBC) presented with a twelve-month history of skin thickening and tightness across his chest. After a skin biopsy and immunological investigations, a diagnosis of generalised morphoea (GM) was made. His GM markedly improved with nine months of colchicine therapy. To our knowledge there have been only two previously reported cases of PBC associated with GM. Difficulties with treatment of GM are discussed.

66歲華人男患者患有原發性膽汁性肝硬化，於其胸部呈現皮膚增厚及繃緊達12個月。經皮膚組織活檢及免疫檢查確診為不定型硬皮病。患者的不定型硬皮病經9個月秋水仙鹼治療明顯好轉。就我們所知，迄今祇有兩例原發性膽汁性肝硬化伴發不定型硬皮病的報導。不定型硬皮病治療方面的困難將予討論。

**Keywords:** Anxiety, colchicine, functional impairment, generalised morphoea, primary biliary cirrhosis, skin thickening

**關鍵詞：**焦慮，秋水仙鹼，機能上的障礙，不定型硬皮病，原發性膽汁性肝硬化，皮膚增厚

## Introduction

Although generalised morphoea (GM) is a type of scleroderma, it is essentially a skin disease and

systemic involvement is usually absent. It can be distinguished from systemic sclerosis by the absence of Raynaud's phenomenon, acrosclerosis and internal organ involvement.<sup>1</sup> However, there have been several case reports of GM associated with systemic diseases, including idiopathic thrombocytopaenia,<sup>2</sup> necrotising vasculitis,<sup>3</sup> polymyositis,<sup>4</sup> acral cutaneous myofibroma<sup>5</sup> and primary biliary cirrhosis (PBC).<sup>6,7</sup> To our knowledge there have only been two reported cases of PBC associated with GM to date.<sup>6,7</sup> We report a case of PBC in a patient with GM.

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## Case report

A 66-year-old Chinese male was referred by his gastroenterologist because of a twelve-

month history of skin tightening and a burning sensation across the chest. He also experienced breathing discomfort and reduced exercise tolerance. He was not on any regular medications. There was no history of hepatitis and he did not drink alcohol.

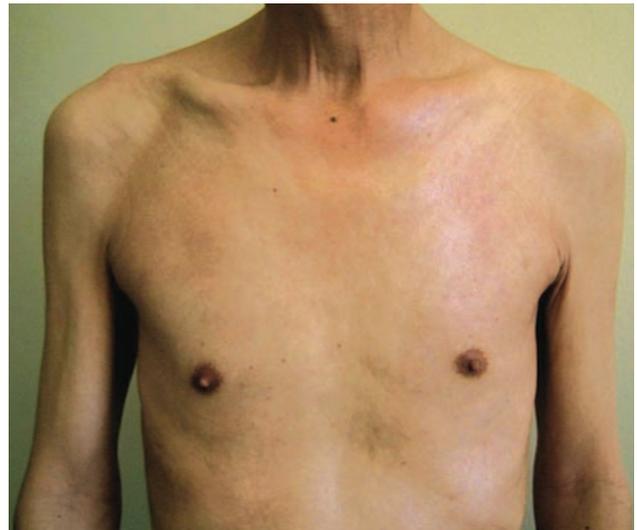
During this time, a diagnosis of PBC was made by the gastroenterologist on the basis of a positive antimitochondrial antibody titre of 160 (normal <10) and abnormal liver function tests which included an alkaline phosphatase of 496 U/L (normal 30-115 U/L), gamma glutamyl transferase of 377 U/L (normal 0-45 U/L), alanine aminotransferase of 75 U/L (normal 0-40 U/L), and aspartate transferase of 63 U/L (normal 0-40 U/L). His bilirubin was normal at 11  $\mu\text{mol/L}$  (normal 0-20  $\mu\text{mol/L}$ ). The patient declined a liver biopsy as he was concerned about the risks of the procedure. His abdominal ultrasound and CT cholangiogram showed no abnormalities. He was commenced on oral ursodeoxycholic acid for his hepatic problem, and the liver function tests markedly improved three months after the treatment was commenced, with a reduced alkaline phosphatase of 254 U/L and gamma glutamyl transferase of 88 U/L.

On cutaneous examination, there was a confluent area of skin thickening and tightness on his neck and shoulders, extending down to his epigastrium in an inverted triangle pattern, with distinct demarcation between thickened skin and normal skin (Figure 1). Some areas of hyperpigmentation and ivory discolouration were observed. No other areas of involvement were detected clinically.

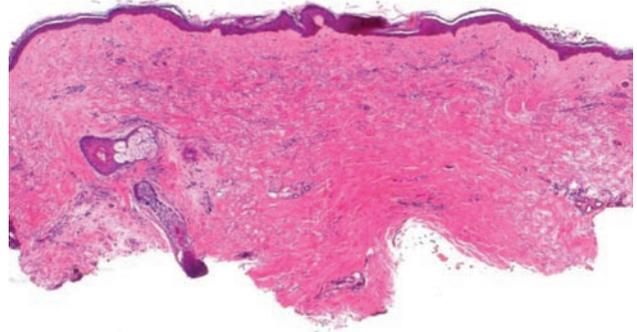
Serological investigations revealed a positive antinuclear antibody (ANA) with a titre of 1:160 (normal <1:40) and an atypical speckled staining pattern, negative anti-neutrophil cytoplasmic antibody (ANCA), negative anti-extractable nuclear antigen (ENA) antibodies including anti-Scl-70 antibody, and negative anti-smooth muscle antibody (ASMA).

A skin biopsy showed epidermal atrophy and abundant thick collagen bundles in the dermis extending deeply around eccrine glands. These changes were reported to be consistent with morphea (Figure 2). Lung function tests did not show evidence of restrictive lung disease.

The patient was commenced on colchicine 500 micrograms twice daily for his GM. Two months



**Figure 1.** Generalised morphea, before colchicine therapy.



**Figure 2.** Histopathology showing epidermal atrophy and thickened collagen bundles in the deep dermis. (H&E, low power view).

later, the colchicine dosage was reduced to 500 micrograms daily due to diarrhoea. After nine months of colchicine therapy his GM improved markedly (Figure 3). Furthermore, there was much less skin tightness, reduced burning sensation and increased exercise tolerance. Several years after colchicine therapy has been completed, we are pleased to report that the patient's GM remains dramatically improved.

## Review

It would be helpful to be consistent with nomenclature in managing patients with morphoea. Using the term "localised scleroderma" can be confusing to both patients and practitioners. Some patients become unnecessarily depressed and anxious after reading that scleroderma patients may die of internal organ failure. Accordingly, even though we are unable to cure morphoea, providing a precise explanation and giving hope and support to patients with disfiguring morphoea will, at least, allay their fear.

Morphoea is not a common or life-threatening dermatosis. Nevertheless, it can be a source of



**Figure 3.** Generalised morphoea, much improved after nine months of colchicine therapy.

anxiety and embarrassment. Many patients are young women, and not uncommonly the skin lesions are in cosmetically important areas. Although morphoea tends to improve slowly over time, unfortunately, spontaneous improvement usually takes at least several years. At times, the cosmetic problem can be much more long lasting.

PBC is a result of chronic inflammation and fibrous obliteration of intrahepatic bile ductules, causing cholestasis.<sup>8</sup> Dermatological disorders reported to occur in association with PBC include CREST syndrome,<sup>8</sup> cutaneous granulomata,<sup>9</sup> bullous pemphigoid,<sup>10</sup> pyoderma gangrenosum,<sup>11</sup> lichen planus,<sup>12,13</sup> vitiligo<sup>14</sup> and GM.<sup>6,7</sup> The aetiology of PBC remains unknown. However, frequently reported associations of PBC with a variety of disorders presumed to be autoimmune in nature are suggestive of an autoimmune process in its pathogenesis. These associated disorders include CREST syndrome, sicca syndrome, autoimmune thyroiditis, type 1 diabetes mellitus and IgA deficiency.<sup>8</sup> Most patients with PBC are asymptomatic and the diagnosis is often made on routine liver function tests. Even though the majority of these patients remain asymptomatic for a long period, many ultimately develop progressive liver disease.<sup>8</sup>

The aetiology of GM is also unknown. It was previously suggested that GM might have a common pathogenesis with PBC, based on the fact that GM is one of the most common manifestations of chronic graft-versus-host disease, and PBC is known to have liver histology resembling chronic graft-versus-host disease.<sup>6</sup>

Clinical and laboratory findings of previously reported cases, together with this current case, are summarised in Table 1. In all three cases, primary PBC investigations were initiated following the incidental finding of abnormal liver function tests. One case had occasional pruritus for five years before the diagnosis of PBC, and this may be explained by PBC. However, other cases had no symptoms due to PBC. Duration of GM before

**Table 1.** Clinical and laboratory findings of previously reported cases and current case

Reference	Age	Sex	Areas affected by GM	Reason for PBC investigation	Symptoms due to PBC	Duration of GM before the diagnosis of PBC	AMA (titre)	ALP (U/L)
Suyama, et al <sup>6</sup>	50	Female	Neck, upper chest, lower abdomen, back, lumbar region	Abnormal LFT	Occasional pruritus (could be due to PBC)	5 years	320	192
Natarajan, et al <sup>7</sup>	58	Female	Trunk, limbs	Abnormal LFT	Nil	7 months	800	253
Current case	66	Male	Neck, shoulders, chest, upper abdomen	Abnormal LFT	Nil	12 months	160	496

GM: Generalised morphoea, PBC: Primary biliary cirrhosis, LFT: Liver function test, AMA: Antimitochondrial antibody, ALP: Alkaline phosphatase

diagnosis of PBC varied between seven months and five years. All the cases had high titres of antimitochondrial antibody and markedly raised alkaline phosphatase, which are consistent with PBC.

A liver biopsy could have been performed to confirm the diagnosis of PBC in this case. However, the diagnosis of PBC was strongly supported by positive antimitochondrial antibody with a high titre, which is both sensitive and specific;<sup>8</sup> raised alkaline phosphatase and gamma glutamyl transferase; a normal abdominal ultrasound and a normal CT cholangiogram. Marked response to ursodeoxycholic acid is also consistent with the diagnosis of PBC.

Treatments to date have shown only little proven benefit for GM, despite trials with penicillamine, antimalarials, phenytoin, colchicine and systemic corticosteroid.<sup>1</sup> Our patient responded well to colchicine. Colchicine is a unique anti-inflammatory agent that is effective against gouty arthritis. It inhibits the migration of granulocytes into areas of inflammation. Moreover, it is a relatively safe and cheap medication, with diarrhoea being a frequent side effect. Serious side effects, including pancytopenia and renal failure, occur rarely.<sup>15</sup> Colchicine was tried in our

patient because of previously reported benefits in both GM and PBC,<sup>1,8</sup> its low side-effect profile and good tolerance by the patient.

Colchicine has been reported to be effective in various neutrophilic dermatoses, including psoriasis, Behçet disease, necrotising vasculitis, urticarial vasculitis, Sweet syndrome, palmoplantar pustulosis, dermatitis herpetiformis and adult linear IgA bullous dermatosis.<sup>16</sup> It was suggested that colchicine is effective for these disorders through its anti-inflammatory effects mediated by inhibition of neutrophil and monocyte chemotaxis and leucocyte adhesiveness.<sup>17</sup> Colchicine was also shown to arrest cell division *in vivo* and *in vitro*. It arrests mitosis in metaphase by stopping spindle formation, and affects cells with the highest rates of mitosis earliest.<sup>15</sup> We speculate that colchicine is effective in GM by arresting cell division of fibroblasts with high rates of mitosis.

The response to treatment and ongoing assessment of GM are difficult due to the lack of an objective assessment method. Lung function testing was conducted in our case to assess possible restrictive lung disease secondary to the mechanical effect of GM. It would be ideal to have an objective method to assess the extent of GM and monitor response to therapy, like the one used

for the burns patients' assessment. For example, assessment can be conducted by grading skin thickening according to skin elasticity and estimating percentage of body area involved. A new dynamic testing device has been developed to assess skin stiffness and viscoelasticity. This device may prove to be invaluable in the future.

It is generally accepted that the exact aetiology of GM is not clearly understood. Even so, our case raises the likelihood of autoimmunity being pathogenetically important because of its association with PBC. Moreover, our case raises the possibility of colchicine being an effective treatment for GM. Finally, even if the clinical improvement was not solely due to colchicine, we have given our patient hope and the reassurance that GM can be improved: no morphea could well mean 'no more fear'!!

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