CASE REPORT

Following leads: connecting dysphagia to mixed connective tissue disease

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SUMMARY

Mixed connective tissue disease (MCDT) is a rare condition characterised by the presence of high titres of anti-U1 ribonucleoprotein antibodies and selected clinical features of systemic lupus erythematosus, systemic sclerosis and polymyositis/dermatomyositis. Early symptoms are non-specific, including easy fatigability, myalgia, arthralgia and Raynaud's phenomenon. Some reports emphasised the favourable outcome and excellent response to glucocorticoids, but there are contradictory studies reporting worse prognosis. Also, a subset of patients evolve into a clinical picture more consistent with a major diffuse connective tissue disease. We present the case of a 50-year-old black woman whose inaugural presentation of MCDT was oropharyngeal dysphagia, symmetrical proximal muscle weakness, tongue atrophy and skin sclerosis. High-dose corticosteroids and methotrexate were given with little improvement, maintaining disabling dysphagia leading to a percutaneous endoscopic gastrostomy tube placement. She was then started on intravenous immunoglobulin with progressive remission of symptoms.

BACKGROUND

Dysphagia is usually attributable to benign disease processes, but it is also a cardinal symptom of several malignancies. Mixed connective tissue disease (MCDT) is not usually a first hypothesis when one considers dysphagia. In fact, MCDT is an infrequent disorder with a prevalence of 3.8 per 100 000 adults and an incidence of 2.1 per million per year, taking into consideration data from a 2011 nationwide study in Norway.[1] Myositis develops in 80% to 90% of patients, being mainly subclinical.[2] Severe clinical muscle weakness is unusual with only four reports of severe myositis described in literature.[3 4] Typically, it improves with corticosteroids, but some patients need cytotoxic therapy. This case represents an example of an uncommon cause of dysphagia that one should keep in mind, given its difficult management and morbi-mortality. It also raises awareness to ongoing discussion on prognosis.

CASE PRESENTATION, INVESTIGATION, DIFFERENTIAL DIAGNOSIS AND TREATMENT

We report the case of a 50-year-old black woman with arterial hypertension and obesity who had been reporting polyarthralgia and Raynaud's phenomenon for 2 years. She had no other symptoms, despite positive antinuclear and anti-U1 ribonucleoprotein (U1-RNP) antibodies. She presented to the emergency department with rapidly progressive non-selective dysphagia, weight loss and disabling continuous sialorrhoea (with 1 month evolution). Clinically, she was hypoglycaemic (42 mg/dL), had symmetrical proximal muscle weakness with muscle strength graded as 3 on deltoid and hip flexors, tongue atrophy, hand oedema (figure 1), salt-and-pepper facial pigmentation and sclerosis (figure 2), skin sclerosis affecting hands and forearms (figure 3), and oropharyngeal dysphagia. For nutrition, nasogastric intubation was necessary in addition to introduction of butylscopolamine, amitriptyline and atropine for sialorrhoea management. Our focus was on dysphagia, namely finding out if there was a structural or a propulsive anomaly responsible for it. Obstructive causes were excluded after performing an upper endoscopy and cervical CT, while central neurogenic causes, mainly stroke and brainstem lesions, were excluded after a neurology consult and head MRI. Oesophageal biopsies showed congestion and mild inflammatory infiltrate compatible with mild oesophagitis. Blood workup revealed an elevated erythrocyte sedimentation rate (maximum value of 54 mm/1st hour (N<30)), elevated creatine kinase (4087 IU/L (N 26–192)), myoglobin (1073 µg/L (N 19–51)) and aldolase (30 IU/L (N<8.8)), normal thyroid function, fasting glucose and glycated haemoglobin and negative anti-acetylcholine receptor antibody. Therefore, thyroid disease, diabetes and myasthenia gravis were excluded. Later on, the laboratory studies confirmed positive antinuclear antibodies with a speckled pattern and titre superior to 1/640, positive anti-U1-RNP antibodies, normal complement and negative rheumatoid factor, anti-citrullinated protein, antiphospholipid, anti-Jo 1, anti-PM/ScL, anti-Scl 70, anti-centromere, anti-Sm, anti-SSA/SSB, anti-histone and anti-nucleosome antibodies.

Considering the previous history of polyarthralgia and Raynaud's phenomenon with positive anti-U1-RNP antibodies, currently accompanied by scleroderma-like features (namely skin fibrosis and oesophageal dysmotility) and myositis, the hypothesis of mixed connective tissue disease versus systemic progressive sclerosis was raised. Further studies were performed in order to clarify the diagnosis. Oesophageal manometry revealed absent peristalsis in the whole oesophagus, whereas electromyography demonstrated myopathic changes of upper muscles. Nailfold capillaroscopy showed giant capillaries, petechial haemorrhage

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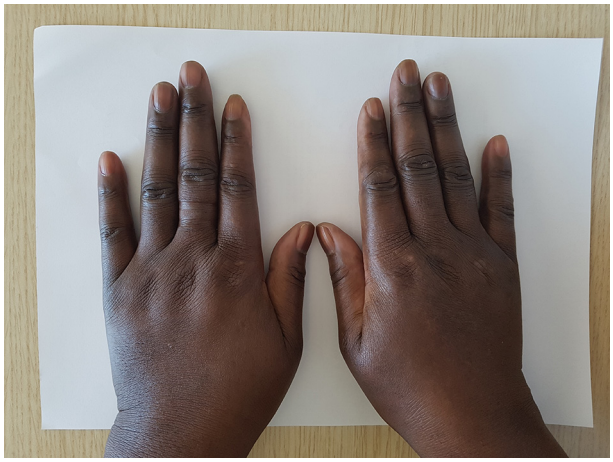

Figure 1 'Puffy fingers'.

Figure 3 Skin induration on forearms.

and neoangiogenesis, overall compatible with early scleroderma pattern (figure 4) and secondary Raynaud's phenomenon. Fulfilment of serological criteria plus more than two clinical criteria allowed the diagnosis of mixed connective tissue disease.[2] Severe myositis was the central feature, so she was started on high-dose corticosteroids and methotrexate. Unfortunately, there was little improvement, as she maintained disabling dysphagia and sialorrhoea. Therefore, a percutaneous endoscopic gastrostomy (PEG) tube was placed. Following a multidisciplinary discussion of the case, intravenous immunoglobulin (IVIG) was then tried (2-day intravenous pulses at 0.4 g/kg/day).

Lung function tests, as well as urinary protein:creatinine ratio, were normal. The echocardiogram showed mild pulmonary hypertension. Thoracoabdomino-pelvic CT, mammography, endovaginal ultrasound and thyroid ultrasound were all normal, excluding underlying malignancies.

OUTCOME AND FOLLOW-UP

She was discharged 29 days after admission on prednisolone (60 mg/day) and methotrexate (20 mg/week), maintaining enteric nutrition through PEG tube. She was referred to the Autoimmune Diseases Clinics and administration of IVIG pulses was repeated twice. Progressive improvement was observed with remission of symptoms and CK normalisation. Corticosteroids were tapered and the PEG tube was removed 3 months after, with normalisation of weight and feeding habits. Oesophageal manometry performed 9 months after showed improvement, still maintaining inefficient oesophageal motility. Concomitant nailfold capillaroscopy also demonstrated fewer haemorrhage spots and dilated capillaries, maintaining the pattern previously described. Nowadays, she is on methotrexate and asymptomatic, maintaining close monitoring.

DISCUSSION

MCDT was originally defined by Sharp in 1972 as an overlap syndrome characterised by the presence of high titres of antibody to extractable nuclear antigens (ENAs) and selected clinical features of systemic lupus erythematosus (SLE), systemic

Figure 2 Salt-and-pepper face pigmentation corresponds to areas of hyperpigmentation and hypopigmentation.

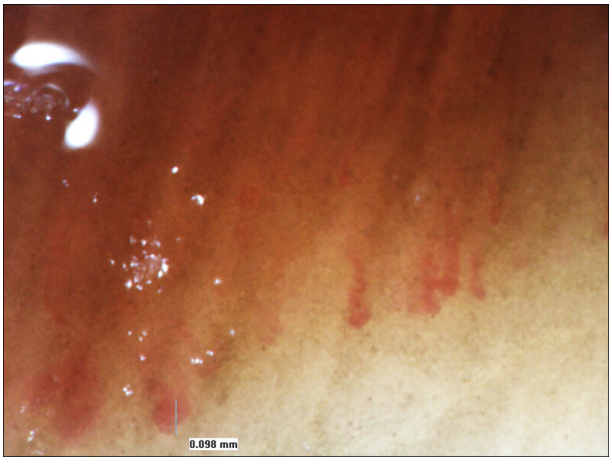

Figure 4 Architectural disorganisation and giant capillaries observed in one of the nailfold capillaroscopy images.

sclerosis (SSc) and polymyositis/dermatomyositis (PM/DM). ENA has since then been determined to be U1-RNP and the presence of these antibodies is the hallmark of MCTD. U1-RNP antibodies consist of RNA plus three proteins (A′, C′ and a 68–70 kDa protein).[5 6] Pathogenesis remains unknown, but some studies have suggested a pathogenic role for U1-RNP. Recent data have reinforced the notion that the autoantibody production may be genetically determined and driven by distinct subsets of human leukocyte antigen-restricted T cells. HLA-DR4 and DR1 are associated with MCTD. Other pathophysiological abnormalities that are believed to play a role include B-lymphocyte hyperactivity, resulting in high levels of anti–U1-RNP and anti–U1-70 kDa autoantibodies; T-lymphocyte activation, with anti–U1-70 kDa–reactive T lymphocytes circulating in the peripheral blood; apoptotic modification of the U1-70 kDa antigen; and immune response against apoptotically modified self-antigens.[2 7]

It is an uncommon disease, as previously mentioned, with a female-to-male ratio of 3.3 up to 8 in recent studies. The disease appears in all age groups, but the peak incidence is around 40 years old.[1 2] To date, there are no uniform guidelines or international consensus on how, when and in whom MCDT should be diagnosed. Patients present with overlap clinical manifestations of SLE, PM/DM and SSc. In the early phase, many patients complain of easy fatigability, myalgia, arthralgia and Raynaud's phenomenon. Nowadays, we know that every major organ system can be involved during the course of the disease. Skin involvement occurs in most patients with Raynaud's phenomenon as the presenting feature, but hypopigmentation/hyperpigmentation and scleroderma can also be present, similar to our patient's presentation. Vasculopathy is similar to SSc and is characterised by bland intimal proliferation and medial hypertrophy that affects small and medium-sized vessels, also responsible for pulmonary arterial hypertension. Nailfold capillaroscopy changes are similar to those found on SSc, although the presence of dystrophic, 'bushy', capillaries, consistent with angiogenesis, is reported to be characteristic of MCTD, as we observed in our patient. Cardiovascular involvement varies between 11% and 85%, depending on the method used to detect. There is also increasing recognition and concern for accelerated atherosclerosis and cardiovascular events, a feature of most autoimmune diseases. Pulmonary abnormalities are found in up to 85% of patients, such as interstitial lung disease and pulmonary arterial hypertension. Originally, absence of renal disease was a hallmark of MCDT, but follow-up studies have indicated that up to 20% of patients eventually will develop some form of renal disease. Severe central nervous system involvement is rare. Gastrointestinal disease is common (66%–74%) and often represents a major feature of overlap with SSc. Oesophageal dysfunction is the most prevalent manifestation with heartburn and dysphagia being the most common symptoms. Depending on the studies, dysphagia can present in up to 53% of patients, but abnormal oesophageal manometries occur in up to 85% of patients who are asymptomatic. Oesophageal biopsies show atrophy, loss of smooth muscle cells and fibrosis on the muscular layer of the lower oesophagus, as well as immunoglobulin and complement deposition. Between 80% and 90% of patients develop muscle disease with only subclinical increase in muscle enzymes. This inflammatory myopathy is clinically and histologically identical to PM/DM, although focal myositis may occur. Only 2%–3% of patients present with myositis in the initial stages, and frank myositis with significant weakness, electromyographic abnormalities and/or muscle enzyme elevation occurs even less commonly. The distribution of weakness is characteristically symmetrical and proximal with affection of the deltoids and hip flexors. Usually, patients report a history of insidious development of muscle weakness with gradual worsening over a period of time.[2 8–14]

As previously described, our patient had oesophageal aperistalsis and mild esophagitis on oesophageal biopsies; therefore, myositis was the one causing dysphagia. The association of dysphagia in patients with MCDT and myositis was described by Gutierrez *et al*[15] and is due to the involvement of the oesophageal striated muscle.

Regarding diagnosis of MCDT, most physicians would agree that it should be considered in an anti-U1-RNP-positive patient presenting with Raynaud's phenomenon, 'puffy hands' and at least two of the following clinical features: arthritis, myositis, leucopenia, oesophageal dysmotility, pleuritis, pericarditis, interstitial lung disease or pulmonary arterial hypertension. We can also follow one of the four coexisting criteria sets: Sharp, Alarcón-Segovia, Kasukawa and Kahn.[2] However, some clinicians argue that MCDT does not exist and consider it an overlap syndrome. Overall, diagnosing MCTD in clinical practice is an issue of pattern recognition and clinical decision. As previously mentioned, our patient fulfilled all the criteria for MCTD: she had high titres of anti-U1-RNP antibodies, polyarthralgia, Raynaud's phenomenon with typical MCDT nailfold capillaroscopy pattern, diffuse hand oedema, scleroderma, oesophageal dysmotility on manometry and myositis with elevated muscle enzyme levels and electromyographic abnormalities. Reviewing previous history and findings, we can assume that the disease had been progressing over some time, given the previous sclerodermatous manifestations. Indeed, a nationwide Norwegian study in juvenile-onset MCTD found out that inflammatory presentations, such as myositis, arthritis and serositis, decrease over time and the more fibrotic scleroderma-like features increase with disease progression. Furthermore, up to 50% of patients evolve to another connective tissue disease over a period of 10 years. The presence of anti-DNA antibodies is associated with evolution into SLE, and oesophageal dysmotility and sclerodactyly with evolution into SSc.[16–18]

But, if there are no consensual guidelines, how do we treat patients with MCDT? Therapy should be individualised for each patient to address the specific organs involved and the severity of the underlying disease activity. Focusing on our case, we found only four cases of severe myositis in the literature, detailing patient improvement after high-dose corticosteroids and methotrexate.[3 4] Our patient did not follow the same course and was steroid resistant. As there are no guidelines or protocols regarding resistant myositis treatment in MCDT, physicians follow previous experience from PM/DM. Some authors recommend association of high-dose IVIG, while others prefer rituximab. After a multidisciplinary discussion, IVIG was the choice, given our physicians' previous experience. The clinical improvement was notorious, requiring only three courses of IVIG in total.[2 13 19–21]

The original description of patients with MCTD emphasised the relatively good prognosis and excellent response to glucocorticoids, but follow-up studies have showed otherwise. Approximately one-third of patients have a benign course and go into remission, one-third have a more aggressive course with less favourable response to treatment and the remaining have a partial response but still require immunosuppressive therapy after several years.[18] Our patient seems to fit in an in-between category: she had an aggressive inaugural presentation, not responding to corticosteroid and cytotoxic therapy, but after implementation of IVIG she had a partial response, despite still needing therapy with methotrexate. And what about her prognosis? In the literature, the largest study of mortality in patients

with MCTD reported survival rates of 98%, 96% and 88% at 5, 10 and 15 years after diagnosis among 280 patients. The major causes of death were pulmonary arterial hypertension, severe infection, cardiovascular events, cancer and thrombotic thrombocytopaenic purpura.[8 14 16 18] Favourable outcome was observed with clinical remission and significant reduction of U1-RNP antibodies titres.[18] Conversely, higher titres of U1-RNP antibodies, presence of anticardiolipin, anti–β_2-glycoprotein and antiendothelial cell antibodies, positive rheumatoid factor, antiphospholipid syndrome, serositis and pulmonary arterial hypertension were associated with worse prognosis.[2 8 14 17–19] Our patient is nowadays in clinical remission, but there is cause for concern: her inaugural presentation was that of an aggressive disease, she maintains high titres of anti-U1-RNP antibodies and still has important oesophageal dysmotility, which has been linked to interstitial lung disease.[11 16] Furthermore, morbidity is quite high, given recurrent symptoms, the stress of living with a potentially fatal condition and the long-term consequences of therapy with either steroids or cytotoxic drugs.[19]

This case raises some important questions concerning follow-up: how can we predict clinical remission? Therapy choice on flares? Should we keep looking for malignancy? How can we prevent disease progression? And, finally, will there be a progression into another major connective tissue disease and, if so, how will it alter her clinical course? This case reinforces the need for a multidisciplinary approach, risk stratification and prognosis prediction.

Learning points

- Mixed connective tissue disease is characterised by the presence of high titres of anti-U1 ribonucleoprotein (U1-RNP) and overlap features from systemic lupus erythematosus, systemic sclerosis and polymyositis/dermatomyositis.
- Diagnosis is an issue of pattern recognition and clinical decision, but it should be considered in an anti–U1-RNP-positive patient presenting with Raynaud's phenomenon, 'puffy hands' and at least two of the following clinical features: arthritis, myositis, leucopenia, oesophageal dysmotility, pleuritis, pericarditis, interstitial lung disease or pulmonary arterial hypertension.
- Therapy should be individualised for each patient to address the specific organs involved and the severity of the underlying disease activity.
- Outcome depends on disease activity and complications, namely pulmonary arterial hypertension.

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