

Clinical Reasoning: A 49-year-old woman with progressive motor deficit

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SECTION 1

A previously healthy 49-year-old woman presented with progressive motor deficit. The complaints started the year before with weakness of the right arm. Over the subsequent months, she developed weakness in the left arm, followed by both legs, and, finally, difficulty speaking, with nasal voice, and swallowing. It was increasingly difficult to attend to her chores, and, by the time she sought medical attention, she needed help with all daily activities. In the last few weeks, she also complained of diffuse joint and muscle pain. Medical and family history were unremarkable.

Neurologic examination showed bilateral facial weakness, severe dysarthria, dysphonia and dysphagia (nasal reflex preserved), decreased shoulder elevation

strength, and difficulty protruding the tongue, without fasciculations or atrophy. Symmetrical tetraparesis (proximal-greater-than-distal weakness) and increased tone were noted, with severe pain upon mobilization and palpation of joints and muscles. Deep tendon reflexes were brisk and symmetric, with bilateral flexor plantar responses. There was atrophy of the interosseous muscles of the hands and shoulder girdle muscle wasting.

Questions for consideration:

1. How do you localize the symptoms: upper motor neuron (UMN) or lower motor neuron (LMN), neuromuscular junction (NMJ), peripheral nerve, or muscle? What is the broad differential?
2. What findings on examination would be helpful?

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SECTION 2

The presentation suggested the presence of bulbar (dysarthria, dysphonia, and dysphagia), LMN (weakness, muscle wasting), and UMN (brisk reflexes, increased tone) symptoms. NMJ disorders were not considered since there was no history of ptosis, extraocular muscle dysfunction, or fluctuating symptoms, although bulbar and proximal muscle weakness are common.

Motor neuron disease (MND) was considered initially. The insidious course, with signs and symptoms compatible with UMN and LMN dysfunction present in one body segment and followed by spread to other segments over several months, was the rationale for this reasoning. However, the pain complaints did not quite fit this diagnosis. Cervical radiculomyelopathy, such as cervical spondylosis, with nerve root compression was considered as a differential, as it could cause the

combination of LMN signs at the level of the abnormality with UMN signs below it. This condition also includes sensory abnormalities and sphincter dysfunction, but these features may be absent. However, the bulbar findings would be harder to explain, although syringobulbia or a foramen magnum tumor could be present, and the arthralgia and myalgia were not accounted for. However, the patient did not complain of occipital or upper cervical pain, early symptoms of foramen magnum meningiomas. Cervical MRI was performed, without abnormalities. The absence of sensory signs, the bulbar symptoms, and the quality of the pain also argued against myelopathy at lower levels, radiculopathy, or peripheral nerve disease. Neuropathic pain is usually continuous or paroxysmal with associated dysesthesia and allodynia. Radicular pain radiates along the corresponding dermatome of the injured nerve. The pain complaints were more congruent with muscle and joint pathology. HIV infection and hyperthyroidism were included in the differential but were negative. Inflammatory muscle disease could be considered given the muscle wasting and weakness and severe myalgia, but the brisk reflexes contradicted this hypothesis. However, anxiety may cause brisk reflexes and their symmetry and the presence of flexor plantar responses could be clues to a nonpathologic nature.

EMG studies were ordered to discern whether nerve, muscle, or NMJ dysfunction was present, and revealed myopathic changes.

On closer inspection, some abnormalities were noted: the patient appeared emaciated; there was marked skin thickening over the face, hands, forearms, and feet; and there were areas of skin hypopigmentation and hyperpigmentation with “salt-and-pepper” appearance. The nose was thin and there was decreasing of frontal and nasolabial skin folds, microstomia, cheek telangiectasias, and sclerodactilia, with contracture of distal phalangeal joints (figure 1). The remaining physical examination was normal.

Questions for consideration:

1. What is the differential diagnosis at this point?
2. What diagnostic testing would you order?

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Figure 1 Abnormalities upon physical examination



(1) Thickening of the skin over the face, hands, and forearms, (2) sclerodactilia and distal phalangeal joint contractures, (3) skin hypopigmentation and hyperpigmentation (“salt-and-pepper” appearance), (4) skin folds diminished, (5) microstomia, (6) telangiectasias, (7) muscle atrophy at the interosseous muscles, and (8) shoulder girdle.

SECTION 3

The investigation was refocused due to these observations. Idiopathic inflammatory myopathy (IIM), namely dermatomyositis, could present skin abnormalities. However, there was no malar or extensor surface erythema, photosensitivity, heliotrope, or Gottron papules suggestive of dermatomyositis. Connective tissue disease, namely systemic sclerosis, would explain the findings upon physical examination.

Laboratory tests revealed normal blood cell counts and elevated erythrocyte sedimentation rate (97 mm/1st hour), creatine kinase (2,399 U/L), aldolase (81 U/L), and myoglobin (620.5 U/L). Immunologic testing revealed positive antinuclear antibodies (titer > 1/1,000); rheumatoid factor, anti-double-stranded DNA, antithyroid, anti-Sm, antinucleosome, antineutrophil cytoplasmic antibodies, anti-SSa,

anti-SSb, anti-Scl-70, anti-Jo1, anti-RNP, anticentromere, and antineuronal antibodies were negative.

Skin and muscle biopsy were compatible with scleroderma and polymyositis, respectively (figure e-1 on the *Neurology*[®] Web site at Neurology.org). There was an extensive endomysial inflammatory infiltrate (predominantly T lymphocytes), atrophic and hypertrophic fibers, necrosis, regeneration, and diffuse sarcolemmal major histocompatibility complex class I expression. Electron microscopy did not show tubuloreticular structures. The diagnosis of systemic sclerosis-polymyositis overlap syndrome was established.

Questions for consideration:

1. Would you order additional testing?
2. What are the treatment recommendations and overall prognosis?

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SECTION 4

Paraneoplastic syndrome was a concern, considering the rapid onset and progression. Although cancer occurs in a minority of IIM cases, the risk of associated malignancy is elevated.¹ Extensive search for occult malignancy was performed. Cervico-thoraco-abdomino-pelvic CT scan revealed a large contrast-enhancing thyroid nodule and signs of pulmonary fibrosis but no adenopathies. The thyroid nodule biopsy showed a benign colloid nodule. Mammography and colonoscopy were normal.

Investigation for end-organ lesions is also mandatory.² ECG and echocardiogram were normal. There was no kidney involvement. Gastrointestinal studies revealed ineffective esophageal motility, hypotensive superior esophageal sphincter, and erosive esophagitis. Polysomnography revealed obstructive sleep apnea and pulmonary function tests showed restrictive ventilatory defect. High-resolution chest CT scan confirmed the interstitial lung disease, with ground-glass opacities in both inferior and medial lobes, septal thickening, and bronchiectasis.

The patient was started on IV methylprednisolone 1 g for 5 days, following oral high-dose corticosteroids, with significant improvement of pain and serum muscle enzyme normalization. Tetraparesis improved progressively, although there was no improvement of bulbar muscle symptoms. In fact, worsening of dysphagia, with aspiration pneumonia, was observed, leading to nasogastric intubation. IV human immunoglobulin (IVIg) was tried without benefit, and the patient was started on methotrexate, with significant improvement of tetraparesis and bulbar muscle involvement, although at discharge there was still need for nasogastric intubation. At the last follow-up 15 months later, she was independent in her daily life activities, with mild dysphonia and the need for percutaneous endoscopic gastrostomy for feeding.

DISCUSSION

An overlap syndrome is a rare entity in which a patient fully develops, simultaneously or sequentially, symptoms of 2 or more autoimmune diseases.³ Scleroderma overlap syndromes are relatively common conditions, with the most common combinations occurring with Sjögren disease, IIM, rheumatoid arthritis, and lupus. Myositis is the most frequent association.^{4,5} In fact, this particular overlap syndrome is considered a distinct clinical entity, scleromyositis.⁶ Criteria for each autoimmune disease must be fulfilled. The diagnosis of polymyositis is based on the Bohan and Peter⁷ criteria: (1) symmetric proximal muscle weakness, (2) myositis on biopsy, (3) increased serum muscle enzymes, and (4) characteristic EMG pattern. New highly sensitive and specific criteria were proposed for systemic sclerosis (≥ 3 of the following): (1) anticentromere, anti-Scl-70, or anti-fibrillar antibodies, (2) bibasilar pulmonary fibrosis, (3) digital joint

contracture, (4) dermal thickening proximal to the wrists, (5) calcinosis cutis, (6) Raynaud phenomenon, (7) distal esophageal hypomotility/reflux esophagitis, (8) sclerodactyly/nonpitting digital edema, and (9) telangiectasias.⁸ Apart from positive antinuclear antibodies (ANAs), no antibodies were detected in our patient. ANA positivity has been demonstrated to be present in a significantly higher percentage of overlap patients (as high as 96.6%) in comparison to primary myositis or scleroderma patients.⁵ Anti-PM-Scl antibodies are considered the serologic marker of the disease.⁹

The presentation raised the possibility for MND, initially biasing the evaluation and emphasizing the importance of careful general physical examination. The distinctive features upon physical examination, with abnormalities consistent with systemic sclerosis, as well as the elevated serum muscle enzymes and the myopathic changes on EMG, helped direct the investigation.

High-dose prednisolone (1 mg/kg/day) for 4–6 weeks until disease control is achieved, followed by a taper to the lowest possible dose, remains the first-line therapy. Caution is advised, however, as high-dose corticosteroids may induce scleroderma renal crisis. In cases with poor or incomplete response to steroids, inability to taper steroid dose, significant side effects, or rapidly progressive muscle weakness (particularly involving respiratory/pharyngeal muscles), azathioprine or methotrexate should be used instead. IVIg can be used in severe disease as a bridge until response to other medications occurs.^{1,9} Also, while polymyositis does not respond to IVIg, overlap myositis may respond to the combination of steroids and IVIg.

Scleromyositis is regarded as relatively benign, with good response to corticotherapy. However, overlap patients' survival is inferior to that of patients with IIM,⁵ and overlap myositis is more resistant to treatment than polymyositis, often requiring 2 immunosuppressants.

Our patient presented several risk factors for poor prognosis, namely the long duration of symptoms before treatment; bulbar, esophageal, and lung involvement; and incomplete response to steroid therapy.¹⁰ The persistence and worsening of dysphagia prompted the use of alternative immunotherapies, with positive results. Favorable prognosis depends largely on early treatment and clinicians should aim for an early diagnosis, since delayed recognition of this rare entity may negatively impact on the effectiveness of the treatment and overall prognosis.⁹

AUTHOR CONTRIBUTIONS

Ana Monteiro: conception and design, data collection, literature search, drafting the article, critical revision of the article, final approval of the version to be published. Amélia Mendes: conception and design, critical revision of the article, final approval of the version to be published. Goreti Nadais: critical revision of the article, supervision, final approval of the version to be published. Fernando Silveira: critical revision of the article, final approval of the version to be published. Lígia Castro: critical revision of the article, final approval of the version to be published.

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