Elderly woman with subacute lower limb weakness and rapid systemic decline

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ABSTRACT
A 74-year-old woman developed bilateral leg weakness, with fluctuating cognitive and systemic symptoms that progressed despite treatment. Her diagnosis was confirmed at autopsy. Her case was discussed at the Edinburgh Clinical Neurology Course 2019 Clinicopathological Conference.

HISTORY
A 74-year-old woman presented in November 2018 with a 1-month history of progressive bilateral leg weakness, 2 weeks of vertigo with nausea and vomiting and 2 kg weight loss with anorexia. She described prior coryzal symptoms, followed by left ear deafness, neck pain worse on flexion and intermittent frontal headache. There had been a possible tick bite a month before. She had been previously well. Her only medication was vitamin D. She was an ex-smoker, drank alcohol in moderation and had not travelled outside Scotland for several years. On examination, she had bilateral arm intention tremor, mild weakness of left hip flexion and extension, with left leg ataxia and a positive Romberg’s sign. Investigations were unremarkable (box 1), and she was discharged with a walking stick. She was readmitted 3 days later with urinary retention, worsening gait, leg cramps and constipation. Her condition progressed over the following week to complete paraplegia, requiring urinary catheterisation, and she had periods of hypotension, constipation and confusion. She was afebrile, rambling and unable to draw a clock face. Her left plantar response was extensor, and the right was mute.

She received Pabrinex, ceftriaxone, amoxicillin and aciclovir. She developed a swinging fever, tachycardia and hypotension. She had a sensory level to T6. Her urine was dark; bloods confirmed acute kidney injury. She developed diarrhoea and received amoxicillin for a confirmed enterococcus urinary tract infection. Serial MR scans of brain and spine showed non-specific multiple white matter changes and a small T5 lesion with likely enhancement (box 1 and figure 1). On week 3 of admission, she became acutely unwell, and her chest X-ray showed left basal effusion; she was treated for a hospital-acquired pneumonia and over subsequent weeks received several antimicrobials including amoxicillin, gentamicin, piperacillin with tazobactam (Tazocin), ceftriaxone, metronidazole, meropenem, doxycycline and vancomycin. Over the following 2 weeks, she had fluctuating cognition, fever, tachycardia, hypotension and increasing oxygen requirements. She drew a clock face accurately on week 4.

She was transferred to a neurology centre on week 5. Lumbar puncture (LP) was repeated. Following systemic and haemodynamic deterioration, she was transferred to the intensive care unit for inotropic support. She received 5 days of 1g methylprednisolone. She had a sacral sore with necrotic skin and surrounding erythema. On week 6, arterial blood gases showed hypoxaemia with a plasma lactate of 4.7 mmol/L (0.6–1.8). She had transient episodes of central chest pain, breathlessness and severe hypertension. ECG showed transient narrow complex tachyarrhythmia. Over the next week, she developed acute thrombocytopenia. Enoxaparin was switched to...
Box 1 Summary of investigations

Blood tests
► Full blood count: normal on admission apart from mild monocytosis (1.26–1.61×10⁹/L). Subsequent normocytic anaemia (haemoglobin 103 g/L), raised white cell count (19.8×10⁹/L) and thrombocytopenia (platelets 39–57×10⁹/L).
► Urea and electrolytes: transient acute kidney injury (creatinine: 211 µmol/L, eGFR: 20) on 30 November 2018. Elevated urea in later stages (15.7–17.5 mmol/L).
► Liver function tests: lactate dehydrogenase: 1143 U/L; albumin: 31 (19.11.18) and 17 (30.12.18); other tests normal.
► C reactive protein: 56–205 mg/L.
► Lactate: 1.5–15 mmol/L. Ferritin: 1166 µgram/L. Normal iron and transferrin. Folate: 2.1 (2.8–20).
► Serum antinuclear antibody 1/80 speckled.

Normal or negative tests
► Early morning cortisol, immunoglobulins and serum free light chains, protein electrophoresis, thyroid function test, serum urate, amylase, vitamin B12, serum ACE, MPO-ANCA, PR3-ANCA, C3, C4 levels, ENA, fixed NMDAR ab, VGKC antibodies, coagulation screen and HIT screen.
► HIV/Borrelia/antitreponemal serology and EBV/CMV/HSV1/HSV2/VZV PCR.
Urine Bence Jones protein: type kappa light chains present in urine <0.03 g/L.

Imaging
► CT scan of head (12 November 2018): early small vessel change only.
► Chest X-ray (15 November 2018): bilateral hilar elevation due to postinflammatory scarring and volume loss in each lung apex. Lungs emphysematous.
► MR scan of brain with gadolinium (19 November 2018): areas of increased signal intensity on T2-weighted imaging bilaterally in the cerebral white matter in the centrum semiovale, most prominent in the right parietal lobe and left frontal lobe, in keeping with areas of small vessel ischaemic change. Normal vascular flow voids demonstrated in the circle of Willis and dural venous sinuses.
► MR scan of whole spine (21 November 2018): normal cord signal with no evidence of focal inflammatory lesion.
► MR scan of brain and spine with gadolinium (5 December 2018) (see figure 1):
  – Brain: multiple white matter hyperintensities and more acute looking in the left parietal lobe. Faint enhancement of this lesion centrally, further loci in right frontal subcortical and deep white matter.
  – Spine: questionable cervical white matter change and small T5 intrinsic cord lesion with likely enhancement.
► Radiologists concluded appearances suggested active inflammatory change rather than small vessel change.
► CT scan of chest/abdomen/pelvis with contrast (23 December 2018): moderate-to-large bilateral pleural effusion, small volume of ascites and widespread subcutaneous oedema in keeping with a positive fluid balance.
► Chest X-ray (2 January 2019): progressive bilateral lower zone consolidation, worse on the right. Moderate right-sided pleural effusion increased from previous.

CSF
► CSF (23 November 2018): opening pressure: 11 cm H₂O. White cell count: 10; red cell count: 311. Protein: 1.41 (small pellet of red blood cells visible after centrifugation). Glucose: 3.1 (plasma: 5). No oligoclonal bands. No organisms seen. Viral PCR negative.
► CSF (21 December 2018): unable to lie flat due to breathlessness; no opening pressure recorded. White cell count: 3; red cell count: 0. Protein: 0.86. glucose: 2.9 (plasma: 5.4) multiple matched oligoclonal bands. No growth. Mycobacteria, viral PCR, mycology and cryptococcal antigen: negative. Cytology: no evidence of malignancy or inflammation.

Microbiology
► Serial blood cultures: negative.
► Urine (23 November 2018): enterococccus species >100 000 cfu/mL. Sensitive to amoxicillin and nitrofurantoin.
► Faeces C&S negative, norovirus, Clostridium difficile, adenovirus, enterovirus and parechovirus negative.

C&S, culture and sensitivities; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; ENA, extractable nuclear antigen; HIT, heparin-induced thrombocytopenia; HSV, herpes simplex virus; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibodies; NMDAR, N-methyl-D-aspartate receptor; PR3-ANCA, proteinase 3 antineutrophil cytoplasmic antibodies; VGKC, voltage gated potassium channel; VZV, varicella zoster virus; XR, X-ray.
We have a 70-year-old woman who was pretty well under-recovery. Professor Adrian Wills

Discussion

went autopsy.

(CNS) disorder of unknown cause, and she under-went autopsy.

DISCUSSION
Professor Adrian Wills

We have a 70-year-old woman who was pretty well but dead within 2 months. I am sure, as we have been banging on throughout this course, it is all in the history. The trouble is, there is so much information, I think there are a lot of red herrings. One must do that Bayesian thing, pick out the things that will be helpful. It is a very subacute story. We know she is an ex-smoker so think of cancers and similar. We know the primary presentation is lower limb weakness. But we know that there were preceding non-specific symptoms: vertigo, nausea, vomiting and deafness. I focused on the deafness; I do not know if I should, but there is not a big list of causes of deafness and this might give me a clue. She was a bit coryzal and had some meningism. We are told she may have had a tick bite, but I cannot believe this is Lyme disease, although they are trying to make me say it is. When they examined her initially, the signs were soft. She had flexion greater than extension problem and a positive Romberg’s: it appears to be a pyramidal presentation. She has a tremor as well, so it is spinal cord at the start and then evolves.

The patient rapidly deteriorated and received multiple courses of antibiotics, including cover for Lyme disease and virtually all bacteria that I could think of, and aciclovir as well. Despite that, she deteriorated. Her weakness worsened; there was a hint of autonomic involvement – constipation and hypertension. She became delirious, encephalopathic with fluctuation. At one stage she could not draw a clock, then she could. As the case progressed, the upper motor neuron flavour strengthened with an extensor plantar on one side. Apart from antibiotics, she received vitamins and corticosteroids, but despite that, she worsened.

The MR scan was abnormal, but it is fairly non-specific. There were some white matter lesions in the brain with a little enhancement, but not much in the way of pachymeningeal involvement. There was subtle signal change in the cord, which fits with some of her symptoms. She had many chest X-rays over the course of her illness, with blunting of the angles, probably pneumonia.

Let’s look at some of the other clues. We are told the lactate was high, and I know they are trying to draw me into mitochondrial disease – I do not think it is mitochondrial disease. We are told never to forget mitochondrial disease, but she is a bit old to be presenting now; she never had anything previously to suggest this.

She had urinary light chains. We recall Bing-Neel syndrome, which is an infiltration associated with Waldenstrom’s macroglobulinaemia, but these patients often have hyperviscosity and you would expect a lot of meningeal involvement, which was not the case here. Her antinuclear antibody is weakly positive, but whose isn’t? Her ferritin was high, but that is an inflammatory marker. If your C reactive protein (CRP) is high, ferritin goes high, I do not think this is neuro-ferritinopathy.

The CSF was ‘sort of’ abnormal. She had it twice. The white count was 10, the protein high and the pellet of blood: I don’t know what that means. But no bands. When she had the second LP, she had bands and she could not lie flat, so I thought her diaphragm was involved, as that is a good marker of diaphragm weakness. The second CSF had improved a bit – whether because of corticosteroids or she was fluctuating I am not sure. CSF protein is still high.

We have all the antibodies, and she had lots of tests. But some things are absent – thinking about paraneoplastic syndrome, we are not told about some of those antibodies. I think they had a good search for vasculitides – systemic vasculitides, including Wegener’s granulomatosis, which sometimes presents with deafness, but I do not think Wegener’s would present like this. She is HIV negative; do not ever forget HIV; we think it is mitochondrial disease. We are told never to draw me into mitochondrial disease – I do not think there are a lot of red herrings. One must do that Bayesian thing, pick out the things that will be helpful.

Going back to basics: where and what are the lesions? The lesions were in the brain, cord, possibly in the eighth nerve (we are not told too much about whether the deafness was sensorineural or conductive). And maybe lungs, but I think probably not.
have a big list of differential diagnoses – inflammatory? infective? paraneoplastic? parainfective? neoplastic? genetic?

I shall first tell you what I think it isn’t. Infections first. It is not Lyme disease. Why not? Because the clinical picture is not right, and she had the right antibiotics for Lyme. The tick bite is a red herring of some proportion. We know about the new enteroviruses, first described in the States, but now over here. Those patients can die but have a lower motor neurone flavour, a polio-like illness, and I do not think this fits. We must always consider sarcoidosis—not infectious but I always think of it along with tuberculosis (TB)—and TB, but the CSF is not right for TB. I would expect meningeal enhancement with sarcoid, which is not present – so it’s not that.

I was drawn to Susac syndrome. There are cases described as Susac affecting the cord, but it would be unfair if it were Susac syndrome without more information about eye involvement. The pattern of MRI lesions is not typical for Susac. You get callosal lesions, but also leptomeningeal enhancement and involvement of deep brain structures, not seen here. Cord involvement in Susac syndrome can occur but is unusual, so… it is not Susac.

Next consideration is Sjögren’s syndrome, another great imitator. Sjögren’s syndrome can present with vasculitis and autonomic involvement. But no mention of xerostomia/sicca syndrome, so I think it is not that.

I learnt that Wernicke’s encephalopathy can present with deafness, but she has been given vitamins (in adequate doses I am assuming) and all the other stuff does not fit.

I was drawn to acute disseminated encephalomyelitis (ADEM), but I don’t like ADEM. If it were ADEM, it would be the Hurst variant, which is really aggressive, you would expect a lot of red cells in the CSF and it is very acute so it is not that.

Paraneoplastic syndromes? That is the sort of thing people say at neurology meetings without really thinking, but unless it is a recognisable syndrome, it is an intellectually lazy option. I do not recognise this as a classical (or even non-classical) paraneoplastic syndrome, so we may dismiss this option.

So, what do I think it might be? I have reduced this to two main options. One is intravascular lymphoma, a difficult condition to diagnose in life. It is a non-Hodgkin’s lymphoma with neurological presentation in two-thirds of patients. It has protein manifestations including deafness, and it does not respond to corticosteroids or antimicrobials. It is also a classic clinicopathological conference (CPC) answer.

The other thing I thought about is a glial fibrillary acid protein (GFAP) disorder. If you get this as a genetic abnormality, it is adult-onset Alexander disease, but when you get the antibodies, you get all these features including tremor, which she had. This can sometimes be associated with a teratoma. Her scans do not look like that of Alexander disease, but when you get the antibody-related IgG GFAP syndrome, you get MRI changes, similar to what she had. Also, these are steroid-responsive often; she did not have swollen discs. I would also be surprised if this diagnosis was made at post-mortem.

Professor Wills’ diagnosis
Intravascular lymphoma. I am sure there are other differentials that I have not thought about, but that is my diagnosis.

Questions from the audience
Audience member: Was there progression on serial MR imaging?
AW: I think there was progression, but never much in the way of enhancement.

Hadi Manji (HM): Like you, I think deafness is an impressive symptom. Being progressive rather than acute suggests an inflammatory process. It was 6 weeks since her admission when she was given steroids, and one suspects that the boat was missed by then. She was dead within 4 weeks of that. I was also thinking Susac, because of the deafness and the MRI changes in a late onset patient.

AW: I was very drawn to Susac, but I just think that would have been a bit of information about the eyes. I know they are not always involved, so maybe that’s me being simple.

HM: And I was thinking about other infections, they didn’t cover for listeria with ampicillin, the other thing that can cause deafness with infection is brucella, but she hasn’t been abroad much. But I went with Susac because of the deafness and the scan. And they didn’t give us the neuromyelitis optica or myelin oligodendrocyte glycoprotein antibodies.

Richard Davenport (RJD): Coming back to Susac, would you expect more response to steroids?

HM: I thought it was so far down the line of her illness, it was 6 weeks since she has been in hospital, stepped down from HDU, then only given steroids, she was dead within a couple of weeks. And I think with Susac, you have to go for plasma exchange and intravenous immunoglobulin, it’s a vasculitic type process.

Colin Mumford (CM): 30 years ago, I was a senior house officer in Newcastle when they were just putting mitochondrial disease on the map. In essence what they said was funny neurology affecting lots of different bits of the nervous system, especially poor vision or hearing, slightly dodgy lactate, and don’t dismiss it as a new presentation in the elderly – and you sort of dismissed it.

AW: Yes I think I have, to be in your seventies and not have a sniff of anything before, it’s got to be very, very unusual.

HM: And it’s very rapid, she’s dead within 8 weeks.
AW: On the other hand, you do get MELAS (mitochondrial encephalopathy, lactic acid and stroke-like episodes) cases that present abruptly …..

HM: But they are more stroke like.

AW: So I may dismiss mitochondrial disease at my peril, but I have to start somewhere.

Adam Zeman: Was there consideration for a brain biopsy?

RJD: Brain biopsy was not considered as she refused further investigations for a few weeks, and she was very unwell by the time she transferred to the tertiary centre.

Neil Archibald: Leptospirosis can cause renal involvement, fever and all sorts of stuff, nothing liver though which you usually expect. Was that on your list?

AW: No. My brain is seriously at risk of exploding here with all the possibilities.

RJD: You can tell from the antimicrobial history that they were thinking of infectious diseases a fair amount.

 Audience member: In my view, infection comes to mind. She had monocytosis from the beginning and a prodromal coryzal illness. I don’t know how much significance we should give her deafness. The type of deafness was not specified, they clearly said that cranial nerves were normal on their second review and we were not given any auditory test results. The case progresses with a spinal cord syndrome with a sensory level, other features were low platelets, and there was a skin lesion. Histoplasmosis can cause this. MR spinal cord showed an intramedullary lesion. They did not specify pattern of enhancement on her MR brain; to towards the end, other features were low platelets, and there was an intramedullary spinal cord lesion. Towards the end, she had multisystem failure with low platelets, which can be hospital acquired infection related but histoplasmosis can present with the picture of rapid onset thrombocytopenia and septic shock.

AW: I did think about histoplasmosis and some of the other conditions like Hand-Schuller-Christian disease but what put me off a bit, and I might be wrong, is I associated haemorrhage. We then have to try and work out why we have this infarction.

If we look at the blood vessels, parenchymal and leptomeningeal – there is something in them (figure 2). And if we undertake immunohistochemical assessment with a B lymphocyte marker, CD20, they light up, and the process was multifocal in multiple brain regions. We used the Agilent clone L26 for CD20, dilution 1:200 with low pH retrieval.

These cells were CD20 immunoreactive, and also PAX5, BCL2, BCL6 and MUM1 immunoreactive. They were Epstein-Barr virus negative. The diagnosis is indeed intravascular large B cell lymphoma.

Audience member: We had a patient who presented similar to this on the background of presumed thymoma and was eventually diagnosed with CNS vasculitis. A few months later, she got worse, when she was found to have lymphoma. The brain changes were caused by a vasculitis secondary to lymphoma. I think the diagnosis of intravascular lymphoma sounds reasonable as this can present like vasculitis with infiltration by lymphoma cells in small vessels everywhere especially CNS and skin. This patient had CNS and skin presentation, which can have a wide differential, but typically intravascular lymphoma is a diagnosis made at postmortem.

RJD: So, you think he got it right.

Audience member: I had a case of intravascular lymphoma, it presents aggressively, but usually, from my limited view, they often have more aggressive MRI scans. Is it possible to have less aggressive changes?

AW: I don’t know.

Audience member: I had a case who presented with a cord problem thought to be inflammatory, then had a haemorrhagic stroke, and we diagnosed intravascular lymphoma. We treated with cyclophosphamide and she eventually got better.

Patrick Kearns: She had an albumin of 17, ascites and pleural effusion. Could she be nephrotic? If this was lymphoma, it is very fast and the scan doesn’t seem terrifically awful. So maybe part of the issue is she ran into problems because she got bad nephrotic syndrome.

RJD: I’m not sure if that was considered in life. Interesting point.

Pathology review by Professor Colin Smith

On postmortem examination, there was not a great deal to see macroscopically, which fits the scans though this is always slightly disappointing for such a florid decline. However, histological examination was much more revealing. We found areas of infarction, mostly subcortical, microscopic areas of infarction with associated haemorrhage. We then have to try and work out why we have this infarction.

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Sections of the alveoli of the lungs, stained again with the B lymphocyte marker CD20 (×20). (B) The atypical lymphoid cells immunoreact with the B-lymphocyte marker CD20 (×20).
Intravascular large B cell lymphoma

Intravascular large B cell lymphoma is a rare form of non-Hodgkin’s lymphoma characterised by preferential intravascular growth of malignant lymphocytes, with an often aggressive and fatal course. Incidence is estimated to be 0.5 cases per 1 000 000 cases per year, affecting wide range of ages (17–88), with median age of diagnosis in the sixth to seventh decade. Men and women are affected equally. Clinical presentation appears to vary according to geographical origin. Cases in Western countries commonly present with neurological and skin involvement, while patients from Asian countries more frequently present with involvement of bone marrow, spleen, liver and haemophagocytic syndrome. The cutaneous variant is associated with better prognosis. Beyond this, clinical variation appears to have little effect on prognosis. B-symptoms (fevers, night sweats and weight loss) are common. A small proportion of intravascular large cell lymphoma are of T cell and natural-killer cell origin.

A meta-analysis of 654 intravascular lymphoma cases reported 52% of patients presented with neurological symptoms. Of this, 61% presented with cognitive impairment, 22% presented with paralysis and 13% with seizures. Visual disturbance, ataxia, stroke-like symptoms, headache, myelopathy, dysarthria, cranial nerve palsy, hearing impairment, vertigo, pituitary failure and movement disorders are some of the other CNS presentations reported. Ischaemia due to vascular obstruction tended to give rise to these symptoms, with multiple or multifocal strokes leading to rapid clinical progression in some cases. Previously reported peripheral nervous system presentations include muscle weakness, bladder involvement, cauda equina and conus medullaris syndromes, neuropathies and polyradiculopathies.

As demonstrated in this case, diagnosis of intravascular large B cell lymphoma is challenging given variation in clinical presentations and lack of specific investigations findings, with more than 50% diagnosed postmortem. Common laboratory findings include anaemia, thrombocytopenia and elevated serum lactate dehydrogenase, beta-2 microglobulin, erythrocyte sedimentation rate and ferritin, and hypoalbuminaemia. Fifteen per cent to 20% of patients showed altered hepatic, renal or thyroid function, while 14% of patients had a monoclonal serum component. Usual investigations include whole-body CT, MR neuroimaging, peripheral blood smears, positron-emission tomography scans but these are often falsely negative. A case series from Quebec reported neuroimaging was falsely negative in 45% of patients with neurological symptoms, and no patients without neurological symptoms had positive neuroimaging. Elevation in CSF protein was common. Five of 17 cases with CNS involvement had cells in CSF suspected but not confirmed, as malignant. Tissue diagnosis is crucial in diagnosis; however, risk associated with brain and spine biopsies needs to be considered. Bone marrow biopsies are frequently negative. Biopsies of involved skin may be diagnostic, but in the absence of lesions, some experts recommend random skin biopsies. A case series reported using muscle biopsies as means to achieve diagnosis. Colchester et al. reported a case successfully diagnosed using nasal biopsy and recommended consideration of nasal biopsy in work up of patients with suspected intravascular large B cell lymphoma.

The mainstay of treatment is with combination chemotherapy. Anthracycline-based chemotherapy with rituximab (eg, R-CHOP) is the most commonly use regimen and is associated with 80% complete response rate and 2-year overall survival higher than 60%, with consideration of CNS penetrating drugs, including intrathecal methotrexate if patients are fit enough to tolerate such regimens. Median survival for intravascular large B cell lymphoma where CNS is the primary site of disease is 14.0 months (0.1–84.0) though this has improved from 6 months in cases reported between 1960 and 1989 to 18 months for cases reported in 2000s. Age ≥70 years old, lactate dehydrogenase ≥700 and CNS as site of initial diagnosis are poor prognostic factors.

CNS lymphoma

CNS lymphoma was another popular diagnosis among audience members, but primary CNS lymphoma is a distinct entity from intravascular lymphoma. Primary CNS lymphoma represent 4% of newly diagnosed primary CNS tumours with an incidence rate of 0.5 per 100 000. Immunodeficiency including HIV infection is a major predisposing factor. Similar to intravascular large B cell lymphoma, focal neurological deficits, cognitive and behavioural symptoms

Figure 3 The lymphoma had disseminated throughout all organs examined. There were neoplastic lymphoid cells in the lung alveoli (A: ×20), myocardial capillaries (B: ×10), liver sinusoids (C: ×10) and renal glomerulus (D: ×20). All slides stained with immunohistochemistry (CD20).
Key points

► Intravascular large B cell lymphoma is a challenging diagnosis that should be considered in people with unexplained rapid neurological deterioration.
► Cognitive symptoms, paralysis and seizures are common neurological presentations.
► Hearing loss, elevated serum lactate dehydrogenase and ferritin and elevated CSF protein can point towards intravascular large B cell lymphoma.
► Obtaining tissue is crucial: brain, spine, skin, muscle and nasal tissue are some potential sites for biopsy.

and seizures are common and develop over weeks. However, symptoms of raised intracranial pressure are also common. In contrast to intravascular large B cell lymphoma, neuroimaging is frequently abnormal, typically a solitary homogenous enhancing supratentorial mass lesion. Eyes, CSF and, rarely, spinal cord, are involved.

CONCLUSION

The diagnosis of intravascular large B cell lymphoma is challenging, yet prompt tissue diagnosis is crucial for treatment, which may improve prognosis.1 4 Intravascular B cell lymphoma should be considered for rapidly progressive otherwise unexplained neurological symptoms especially in the context of raised lactate dehydrogenase and ferritin. Tissue biopsy, including random skin biopsies when skin lesions are not present, muscle biopsy and nasal biopsy should be considered.

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