Letter to the Editor

Occam's Razor or Hickam's Dictum: A Case of Myopathy Double Trouble

Dear Editor,

In clinical practice, Occam's Razor is a principle that can usually be applied to diagnose patients with rare neuromuscular conditions. However, a second aetiology needs to be considered if a single cause cannot account for all the symptoms seen in patients. We report the rare case of a patient who developed acute progressive generalised myopathy associated with fever and eosinophilia shortly after returning from a tropical island endemic for muscular sarcocystosis. Subsequently, she was diagnosed with possible coexistent renal cell carcinoma (RCC)-associated antinuclear matrix protein 2 (antiNXP2) myositis with muscular sarcocystosis. She was successfully treated with immunomodulatory treatment, tumour resection and antiparasitic treatment. She made a full and complete clinical recovery.

Case Presentation

A 35-year-old teacher with no past medical history presented with acute progressive generalised myopathy. She was well before symptom onset. Prior to admission, she had visited Tioman Island in West Malaysia for 3 days. A week after her return, she noted episodic fever on alternate days associated with relapsing-remitting cough, rhinorrhoea and migratory myalgia. Each episode lasted a few hours. Before presenting to our institution 10 days later, she developed severe, generalised myalgia and arthralgia with progressive bulbar, limb and truncal weakness.

On clinical examination, her temperature was 38.1°C and her vital signs were stable. Neurological examination showed mild bifacial weakness with normal tongue and palatal movement. Swallow assessment revealed delayed swallows, reduced laryngeal excursions and mild nasal regurgitation. Neck flexion and extension measured 4/5 on the Medical Research Council Scale for Muscle Strength. Tone and deep tendon reflexes were normal. Proximal muscle power was 3/5 and distal power was 4/5. Cerebellar and sensory examinations were normal. Systemic examination was also normal with no evidence of skin rash, joint tenderness or swelling, muscle tenderness or lymphadenopathy. Abdominal and chest examinations were normal. Serum creatine kinase (CK) was 3264 IU/L but it increased to 10,216 IU/L on day 8 of admission. Needle electromyography of the right deltoid, biceps, quadriceps and tibialis anterior muscles indicated generalised, irritable myopathy. The laboratory investigations are summarised in Table 1.

In view of her eosinophilia, recent travel history and relapsing-remitting symptoms, an infective aetiology was considered. While on Tioman Island, she engaged in hiking, snorkelling and had contact with domesticated cats. There was no history of animal bites, sick contact or consumption of uncooked meat or seafood. She was in a monogamous relationship and did not have a history of sexually transmitted diseases. No traditional medication, illicit drug or supplement use was reported.

Serum myositis panel returned strongly positive for anti-NXP2 antibody (EUROLINE Autoimmune Inflammatory Myopathies, EUROIMMUN, Lübeck, Germany). Muscle biopsy showed scattered necrotic and regenerating fibres with no endomysial or perimyseal inflammation. Major histocompatibility complex class 1 expression was upregulated diffusely in the sarcolemma and in some areas of sarcoplasm. Paraffin section showed 2 intrasarcoplasmic, cyst-like structures that contained numerous merozoites (Fig. 1). Subsequent serum specimen showed immunoglobulin G but no immunoglobulin M (IgM) antibody to *Sarcocystis nesbitti* (in-house assay, Department of Medical Microbiology, University of Malaya, Kuala Lumpur, Malaysia). Other systemic blood infective and autoimmune markers tested negative.

Computed tomography (CT) scan of the abdomen, pelvis and thorax showed a left renal lower pole lesion measuring 1.9 × 1.7 × 1.9 cm which showed heterogeneous enhancement, suggesting a hypovascular RCC. There was no radiological evidence of interstitial lung disease.

On day 8 of admission, she was started on parenteral methylprednisolone (1 g/day for 5 days), intravenous immunoglobulin (2 g/kg weight) and oral albendazole (400 mg twice a day for 14 days). A partial nephrectomy and resection of the renal lesion was performed 7 weeks after admission. Histology revealed a localised, chromophobic RCC. Treatment led to rapid resolution of fever and improvement of weakness which were accompanied by normalisation of CK and serum eosinophilia (Table 1). She was treated with a tailing dose of oral prednisolone and was completely weaned off immunosuppressants 9 months

Table 1. Serial Laboratory Investigations

Variable (Unit)	Range	On Admission	Day 8	Day 42	Month 9
WBC count (× 10^3/μL)	4.0 – 10.0	5.2	3.3	10.6	
Haemoglobin (g/dL)	11.5 – 15.0	13.4	12.2	10.4	
Platelet (× 10^3/μL)	150 – 450	267	120	264	
Absolute eosinophil (× 10^3/μL)	0.0 – 0.4	0.6	0.5	0.0	
Absolute neutrophil (× 10^3/μL)	2.0 – 7.5	2.5	7.4	14.7	
C-reactive protein (mg/L)	<10.0	0.6			
ESR (s)	3 – 15	62		39	
Creatinine (μmol/L)	50 – 90	58			
Total bilirubin (μmol/L)	5.0 – 30.0	3.7	2.5	4.7	
ALT (U/L)	10 – 55	117	358	31	
AST (U/L)	10 – 45	151	560	16	
TSH (mIU/L)	0.40 – 4.0	1.0			
FT4 (pmol/L)	10.0 – 20.0	12.6			
CK (U/L)	38 – 164	3264	10,216	62	
ANA, Anti-dsDNA, anti-HMGCR antibody, ENA, RF		Negative			
Extended myositis panel*		Strong positive for NXP2			Negative for NXP2
Dengue IgG/IgM antibody/NS1 antigen, hepatitis A IgG antibody, hepatitis B surface antigen, hepatitis C EIA, hepatitis E IgG/IgM antibody, HIV serology, rubella IgG/IgM serology		Negative			
CMV PCR, parvovirus B19 PCR, serum EBV PCR, tuberculosis T-spot		Negative			

ALT: Alanine transaminase; ANA: Antinuclear antibody; Anti-dsDNA: Antidouble stranded deoxyribonucleic acid; AST: Aspartate transaminase; CK: Creatine kinase; CMV: Cytomegalovirus; DNA: Deoxyribonucleic acid; EBV: *Epstein-Barr* virus; EIA: Enzyme immunoassays; ENA: Extractable nuclear antigen; ESR: Erythrocyte sedimentation rate; FT4: Free thyroxine; HIV: Human immunodeficiency virus; HMGCR: 3-Hydroxy-3-methylglutaryl-*CoA reductase;* IgG: Immunoglobulin G; IgM: Immunoglobulin M; NSI: Non-structural protein 1; NXP2: Nuclear matrix protein 2; PCR: Polymerase chain reaction; RF: Rheumatoid factor; TSH: Thyroid stimulating hormone; WBC: White blood cell

*Qualitative immunoblot assay was performed on EUROLINE kit (EUROIMMUN, Lübeck, Germany) for myositis-associated antigens (IgG) with a titre limit of 1:101 for the following antibodies: EJ, Jo-1, Ku, MDA5, Mi-2a, Mi-2b, NXP2, OJ, PL-7, PL-12, PM-Scl70, PM-Scl100, Ro52, SAE1, SRP and TIF1g.

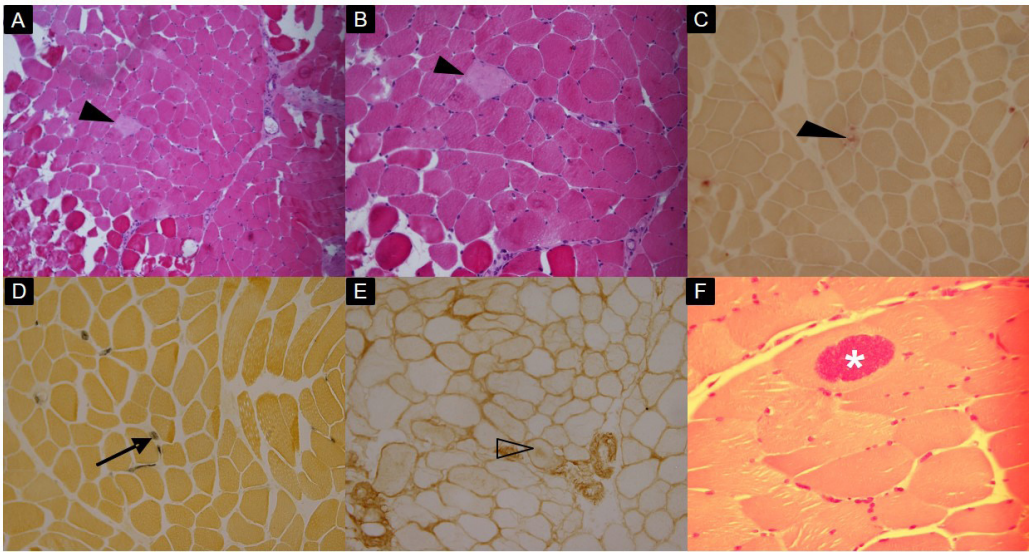

Fig. 1. Left bicep muscle biopsy. A-D: Scanty necrotic fibres (arrowheads) with scattered regenerating fibres (long arrow). Note the absence of a primary inflammatory infiltrate. E: Diffused increased MHC-1 expression of sarcolemma and some areas of sarcoplasm (hollow arrowhead). F: Cyst-like structure (∗) contains numerous merozoites. (A: HE stain, original magnification × 10; B: HE stain, original magnification × 20; C: Acid phosphatase stain, original magnification × 20; D: Alkaline phosphatase stain, original magnification × 20; E: MHC-1 stain, original magnification × 20; F: Paraffin stain, original magnification × 40). HE: Haematoxylin and eosin; MHC-1: Major histocompatibility complex class 1

after presentation. She remained in biochemical and clinical remission 12 months after presentation. Repeat antiNXP2 antibody test at 9 months postsymptom onset was negative.

Discussion

AntiNXP2 antibodies are associated with dermatomyositis and, less commonly, with polymyositis.[1,2] Symptom duration ranges from 2-23 months and fever, myalgia and bulbar, proximal and distal limb weakness are presenting features.[1,3] Serum CK levels range from 1500-26,000 IU/L.[1] Pathological findings include perifascicular atrophy and perivascular inflammation, but these findings are found only in 32% and 53% of 1 patient cohort, respectively.[3]

Although an association with various types of primary malignancies was reported in adult patients,[4] only 1 case of antiNXP2 myositis associated with RCC had been reported.[5] The disappearance of antiNXP2 antibodies following resection of RCC, in tandem with clinical remission, suggests an association between antiNXP2 antibody and RCC in our patient.[6] Although myositis antibodies can be positive in other systemic autoimmune conditions and in infective myopathies, strongly positive myositis antibody levels such as those seen in our patient were shown to be specific in the diagnosis of inflammatory myopathies.[7]

Muscular sarcocystosis secondary to *Sarcocystis nesbitti* has been reported in Tioman Island and Pangkor Island in West Malaysia.[8,9] Snakes are definitive hosts for *Sarcocystis nesbitti* and humans are intermediate hosts.[9] Infection follows consumption of food or water contaminated with faeces of the definitive host. Ingested sporocysts develop in circulating monocytes and blood vessel endothelium before sarcocysts form in the skeletal muscle of the intermediate host.[10] The incubation period ranges from 9-13 days. Early manifestations include fever, headache, joint pain and myalgia while dysphagia and weakness are not prominent features. A relapsing-remitting course is ob-served in more than half of patients. Serum CK is usually elevated to between 200-900 IU/L but it was markedly raised in our patient. Eosinophilia is seen in two-thirds of patients during the course of illness.[9]

A definitive diagnosis is made through histological identification of intrasarcoplasmic sarcocysts. Merozoites are found in a cyst and are encapsulated within a thin membrane. Usually, there is minimal inflammatory change around a cyst.[9,11] In our patient, her serum was non-reactive to IgM antibody to *Sarcocystis nesbitti*, but it must be stressed that current *Sarcocystis* serology is still at an experimental phase. Evidence-based treatment for both muscular sarcocystosis and antiNXP2 myositis is not established. Treatment of muscular sarcocystosis with antiparasitic agents such as albendazole has been attempted with varying results. The mainstay of treatment for inflammatory myopathies involves immunosuppression and, in the case of paraneoplastic inflammatory myopathies, treatment of the associated malignancy. Corticosteroids and steroid sparing agents, including intravenous immunoglobulin, have been used for immunosuppression.

This case highlights several important clinical points. In patients with inflammatory myositis who are seropositive for antibodies associated with cancer, a thorough search for malignancy is mandatory. When a malignancy is found, effective treatment of the underlying malignancy may lead to clinical and serological remission. Additionally, it is important to consider a parasitic aetiology in patients with inflammatory myositis, especially when there is a history of residence in or travel to an endemic region and there is a relapsing-remitting course with associated eosinophilia. Lastly, a second aetiology should be excluded if a single cause cannot account for all the symptoms in patients.

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