Low HbA1c levels in a poorly controlled diabetic

Q1: What do the data demonstrate?
The data demonstrate inappropriately low HbA1c values in a subject with symptomatic hyperglycaemia (weight loss, osmotic symptoms and high plasma glucose values) and abundant glycosuria.

Q2: What is the differential diagnosis and what would you do next?
If a laboratory error can be ruled out (repeated samples need to be obtained), the main differential diagnosis is of an abnormal haemoglobin variant. Some causes of abnormal HbA1c values are listed in Box 1. The next step is to perform haemoglobin electrophoresis. The following results were obtained in this patient:
- Alkalosis: haemoglobin A + J (confirming the presence of abnormal haemoglobin J).
- Globin: fast beta chain variant (normal beta chain).
- Isoelectric focusing: haemoglobin A + J.
- Abnormal haemoglobin: 48% (a high percentage of haemoglobin J).
- Haemoglobin A2: 2.58% (normal <3%).
- Sickle cell: negative (no evidence of sickle cells).
- Haptoglobin: 0.28 g/l (normal 0.7–3.19).

These tests are consistent with a diagnosis of haemoglobin beta chain variant: J trait.

Q3: What is the pathophysiological basis of the discrepancies observed and how would you assess this man’s long term glycaemic control?
Non-enzymatic binding of glucose to the valine residue of the beta chain of the haemoglobin molecule gives rise to glycated haemoglobin (HbA1a, HbA1b, and HbA1c). The level of HbA1c reflects ambient blood sugar concentrations during the life span of the patient’s red cells (half life about 6–8 weeks)—that is, uncontrolled hyperglycaemia results in high HbA1c concentrations during the life span of the patient’s red cells. The following results were obtained in this patient:
- Elevated HbA1c: 0.6% among 15 000 HbA1c estimations in a period of over six years.
- A prevalence of abnormal haemoglobin variants of 0.6% among 15 000 HbA1c estimations.

Abnormal haemoglobin variant.

References

A bed bound patient

Q1: What is the differential diagnosis and the most likely diagnosis?
The differential diagnosis is wide (Box 1, which is not exhaustive) and manifested somewhat by the past medical history. However, the most likely diagnosis is polymyositis. The presentation with proximal muscle tenderness, and importantly weakness, together with a raised ESR and raised creatine kinase is typical. The clinical picture may evolve over several weeks or months, as in this case.

Had the appropriate skin manifestations been present, dermatomyositis would have been an important consideration. Dermatomyositis is easily recognised and diagnosed because of the characteristic rash that may either accompany or precede the onset of muscle weakness. Classically there is a purplish discolouration of the eyelids (heliotrope rash) often associated with periorbital oedema and papular, erythematous, scaly lesions over the knuckles (Gottron’s sign). In addition, a flat, erythematous, sun sensitive rash may appear on the face, neck, and anterior chest (V sign), on the shoulders and upper back (shawl sign), and on the elbows, face, and malleoli. The nail beds often have dilated capillary loops and calcifications may be found in the subcutaneous tissues, although this is much less common in adults than children with this condition.

Inclusion body myositis is characterised clinically by the insidious onset of slowly progressive weakness. The slow evolution of symptoms contributes to the delay in diagnosis, which averages six years. Distinct from polymyositis and dermatomyositis, males are much more commonly affected than females and the clinical hallmark is early weakness of the quadriceps, wrist and finger flexors, and the ankle dorsiflexors. Invariably, the manual muscle scores of the finger and wrist flexors are lower than those of the shoulder and pelvic girdle. Typically the serum creatine kinase is normal or only mildly raised.

The high ESR and the patient’s age in combination with the marked muscle tenderness may point to polymyalgia rheumatica. However, although this condition is characterised by pains and early morning stiffness in the proximal muscles of the shoulder and pelvic girdle, the hands and feet are not affected and there is no muscle weakness. There are also usually some systemic features of a low grade fever or malaise. It is three times more likely diagnosis is polymyositis. The presentation with proximal muscle tenderness, and importantly weakness, together with a raised ESR and raised creatine kinase is typical. The clinical picture may evolve over several weeks or months, as in this case.
common in women than in men and usually occurs between the ages of 60–70 years. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy characterised by a relapsing or progressive course. By definition, symptoms and signs of the neuropathy must be present for at least two months, which distinguishes CIDP from Guillain–Barré syndrome. With a peak incidence in adults of 40–60 years of age, the majority of patients present with symmetric proximal and distal weakness of the arms and legs. Importantly, at least 80% of patients have both motor and sensory involvement, although one may predominate. Although the hyporeflexia seen in this case is compatible with CIDP muscle tenderness would not be expected and the ESR and creatine kinase would typically not be raised. A raised cerebrospinal fluid protein is found in 80%–95% of patients, antibodies directed against myelin proteins are present in a small percentage of patients, and as many as 25% have an IgA, IgG, or IgM monoclonal gammapathy.

This patient’s history of type II diabetes mellitus makes one consider the possibility of a diabetic amyotrophy (also known as diabetic lumbosacral radiculoplexopathy), especially given the pain and the weakness of her quadriceps muscles and the absent knee reflexes. However, this mainly affects men and does not affect the upper limbs. Most patients have no insulin-dependent diabetes mellitus and although commonly associated with periods of poor glycaemic control, the development of this neuropathy is often unrelated to glucose control or the duration of glucose intolerance. In this patient glycaemic control had been good with a glycated haemoglobin (HbA1c) of 6.5%. In diabetic amyotrophy, the neuropathy begins with severe pain in the back, hip or thigh, the pain typically changing as burning, knife-like, and aching. On examination there is weakness of hip flexors and extensors, knee flexors and extensors, and ankle dorsiflexors and plantar flexors of varying degree. Profound atrophy of both thigh and at times distal lower extremity muscles develops.

There are many other metabolic and endocrine causes of proximal myopathy, including hyperthyroidism, myxoedema, Cushings syndrome, acromegaly, osteomalacia, Addison’s disease, and primary hyperaldosteronism. Other conditions such as metabolic disease, myxoedema, Cushings and Addison’s may all be associated with muscle pain at rest and both myxoedema and acromegaly may sometimes result in an increased creatine kinase. In this patient the hormone profile was normal.

A myasthenic syndrome must always be considered in any cause of muscle weakness. It may also cause a mainly proximal muscle weakness, but the lack of demonstrable fatigability and the presence of muscle pain would be atypical. The raised creatine kinase, in this patient, is also against the diagnosis.

Q2: How would you confirm the diagnosis?

The diagnosis of polymyositis would be confirmed by muscle biopsy. Electromyography is usually abnormal in polymyositis with the following features: increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally pseudomyotonic and complex repetitive discharges; small duration, low amplitude, polyphasic motor unit poten-

tials; and motor unit potentials that recruit early but at normal frequencies. However, it can be normal if and uninvolved part of a muscle is sampled.

Muscle biopsy should come from a moderately weak muscle and preferably from a tender area. The predominant histological features in polymyositis are variability in fibre size, scattered necrotic and regenerating fibres, and endomyosal inflammation with invasion of non-necrotic muscle fibres. All of the invaded and some of the non-invaded muscle fibres may express major histocompatibility complex class I antigen which is not normally present in the sarcolemma of muscle fibres. The endomyosal inflammatory cells consist primarily of activated CD8+ alpha, beta T cells, and macrophages. Again, because it can be patchily involved in polymyositis, biopsy can be normal.

Q3: What are the associations of this condition?

It has been known for some time that dermatomyositis and polymyositis are both associated with malignancy. There are some questions remaining as to the exact nature of the association between malignancy and malignancy, the temporal relationship being unclear. In some patients, pre-existing myositis recurs in patients who develop a low diagnosis of malignancy and in patients with a relapse of malignancy, myositis has occurred de novo.”

Dermatomyositis is associated with underlying malignancy especially gastric and lung in men and ovarian and cervical in women. Polymyositis is also associated with a higher incidence of underlying malignancy at the time of diagnosis, but to a lesser extent.” In a large Swedish population-based study the incidence of cancer in patients with dermatomyositis and polymyositis was compared to that in the general Swedish population. In the 392 patients with dermatomyositis the incidence of cancer was 15% (relative risk 2.4 in men and 3.4 in women). In the 396 patients with polymyositis the incidence of cancer was 9% (relative risk 1.7 in men and 1.8 in women).

In addition to the association with malignancy, myositis with secondary congestive heart failure or conduction abnormalities occur in up to one third of patients with polymyositis. Polymyositis has been reported in as many as 45% of patients with cancer at the time of diagnosis. Intestinal and lung disease occurs in approximately 10% of polymyositis patients, at least half of which have to anti-bodies. These are antinuclear antibodies associated with a more moderate response to treatment and poorer prognosis and which are found in around 20% of patients with polymyositis overall. Other antibodies seen in polymyositis include antinuclear antibodies, seen in 16%–40% of cases, and antibodies against the signal recognition particle, found in ~4% of cases and associated with an acute onset of severe weakness, myalgias, and myocarditis.

Q4: How would you manage this patient?

The management of polymyositis can be considered from two main aspects: drug treatment of the disease, general supportive measures, and further investigation of the patient. The mainstay of drug treatment remains corticosteroids especially in controlling the early clinical course. Over 80% of patients at least partially improve, while 10%–35% completely respond to prednisolone.”

Treatment with steroids is usually initiated with prednisolone 0.5 to 2.0 mg/kg per day. Normalisation of muscle enzymes usually occurs within four weeks of commencement of treatment in responders. Improvement in muscle strength occurs later, usually within 3–6 months. Once there has been a full recovery extremely corticosteroids may be gradually reduced (for example, by 5 mg every two weeks). During the period of dose reduction the patient should be monitored closely for evidence of relapse of muscle weakness.

Patients who do not respond to cortico-steroids could be considered for other treat- ment modalities such as intravenous immune globulin, which has been shown to be an effective therapy for drug resistant dermatomyositis and polymyositis.” Methotrexate and azathioprine should also be considered in patients who do not respond well to steroids, patients at risk of steroid side effects and those with poor prognostic indica- tors such as dysphagia, disease duration of three months before treatment, and profound weakness (bed or chair dependence). Metho- trexate is best avoided in patients with coexisting interstitial lung disease and aza- thioprine is contraindicated if there is a past history of high blood pressure and liver function tests every two weeks until a stable dose is reached, and monthly thereafter.

Other treatments being evaluated for use in the treatment of dermatomyositis and polymyositis include plasmapheresis, cyclosporin, tacrolimus, cyclophosphamide, chlorambucil, tumour necrosis factor inhibitors, total body irradiation, and thymectomy.

General supportive measures include good nursing and medical care as well as physiotherapy and rehabilitation. Patients treated with high dose steroids should be given calcium and vitamin D supplementation to prevent osteoporosis. Postmenopausal women should be treated with oestrogen unless contraindicated and bisphosphonates have also been demonstrated to be effective in the prevention and treatment of osteoporosis. There is debate as to the extent that patients with polymyositis should be investi- gated to exclude malignancy. There should be a thorough physical examination with breast, rectal, and pelvic examinations. The full blood picture, ESR, liver function tests, and bone profile should all be recorded. Urinalysis should be performed as well as chest radio- graphy. Testing the myositis antibody profile, blood and gastrointestinal endoscopy may be indicated and women should undergo mammography, pelvic ultrasonography, and have their bone CA-125 levels measured. Further investigation of the patient should be deter- mined by the clinical signs and symptoms. It has been suggested that surveillance for malignancy should continue at annual inter- vals for at least two years after the initial evaluation.”

Discussion

Polymyositis is a non-suppurative inflamma- tory condition of the muscle fibres with evidence of regeneration and inflammation. Generally it presents in patients over the age of 20 years and is more prevalent in females. It may have a very acute presentation and this is often seen in children with polymyositis. The chronic form is characterised by progressive muscle weakness and tenderness. Because there is no associated skin rash, the diagnosis is often delayed when compared with dermatomyositis.

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Polymyositis

Polymyositis generally presents over the age of 20 years and is commoner in females. It is worth noting that only 50% of patients complain of tenderness, weakness being the main complaint. It may be associated with an arthralgia or arthritis. Around one third of cases have dysphagia secondary to oropharyngeal and oesophageal involvement and this appears to be a predictor of poor outcome. Other potential features include Raynaud’s phenomenon and Sjögren’s syndrome.

The histological and immunological features on muscle biopsy suggest that polymyositis is the result of a JILA restricted, antigen specific, cell mediated immune response directed against muscle fibres. The trigger of this autoimmune attack is not known. A viral aetiology has been speculated, but there is no conclusive evidence supporting this theory. The raised creatine kinase together with the raised ESR gave rise to the clinical suspicion of an inflammatory myopathic process in this patient. This was supported by electromyography which showed spontaneous fibrillation and small motor units. However it was muscle biopsy that confirmed the diagnosis of polymyositis. It showed marked necrosis of muscle fibres and loss of muscle fibres (fig 1). However it showed relatively little inflammatory change and this may be due to the length of time before presentation. Our patient was immediately started on oral prednisolone, ranitidine, calcium, and a bisphosphonate.

The difference between polymyositis and dermatomyositis is not merely determined by the presence or absence of a skin rash or the other clinical features listed above. Typically the muscle biopsy features are distinct. In dermatomyositis the characteristic histological finding is of perifascicular atrophy. Although scattered necrotic fibres may be present, in contrast to polymyositis and indeed inclusion body myositis, invasion of non-necrotic fibres is not prominent. In addition, inflammation is predominantly perivascular and located in the perimysium rather than the endomysium, and the infiltrate is mainly composed of CD4+ T cells, B cells, and macrophages.

On initial assessment by occupational therapy and physiotherapy, the patient required the assistance of two persons to stand. Over the next 10 weeks, despite receiving intensive physiotherapy, and a concurrent substantial reduction in ESR (35 mm/hour), there was no improvement in the patient’s clinical condition. It was decided that she was refractory to steroid treatment and she was started on a course of intravenous immune globulin at a dose of 0.4 g/kg over five days. She was also started on azathioprine and after eight weeks of azathioprine treatment in combination with steroids she was mobilising with a walking frame under supervision. Her full blood profile and liver function tests were monitored weekly and regular creatine kinase measurements were made to exclude relapse. Serum creatine kinase can be useful in monitoring response to therapy but only in conjunction with the physical examination. The creatine kinase was raised in patients with normal manual muscle testing, while weak patients can have normal levels.

Overall, this case emphasises the broad range of differential diagnosis. The clinical, biochemical, electro physiological, and pathological markers are typical of polymyositis and this patient demonstrates the clinical response to therapeutic intervention that can be expected in this condition.

Final diagnosis

Polymyositis.

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References


A misleading swelling of the tongue

Q1: What is the differential diagnosis for this lesion?

A possibility of bacterial, fungal, and viral infections should be borne in mind when establishing a differential diagnosis. Tuberculosis, syphilis, histoplasmosis, and actinomycosis are some of the infections which may produce a sarcoïd type of tissue response or granulomas. Other possible entities are foreign body granuloma and oral granulomatous disease as oral Cobin’s disease, granulomas in chelitis, and Meltzer’s syndrome. In this patient our clinical diagnosis was minor salivary gland tumour given the site of occurrence, and hard nodular swelling with overlying normal mucosa.

Q2: How will you establish a definitive diagnosis and suggest the investigations necessary for the same?

Clinical features along with histological evidence of non-caseating epithelioid granuloma from tissue biopsy can be supplemented by chest radiography, the presence of tuberculin anergy, a positive Kviem-Siltzbach skin test, a raised serum angiotensin converting enzyme, anergy, a positive Kviem-Siltzbach skin test, a raised 24 hour urine calcium level is consistent with the diagnosis but is again non-specific.

Final diagnosis

Primary intraoral sarcoidosis.

References

Q2: What other features can be associated with the present clinicoradiological picture?
Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia combine with calcinosis to form the CREST syndrome.

Q3: Which immunological test is positive in a majority of patients with this clinical condition?
Anticentromere antibodies are seen in a very high proportion of patients with CREST syndrome.

Final diagnosis
Calcinosis cutis.

References

Learning points
- Not every discharging sinus is due to infection or malignancy.
- Not all that appears radiopaque on radiographs is solid.
- Examination of hands can provide crucial diagnostic clues even for the lesions in the lower extremity.
- Calcinosis cutis, although more commonly associated with the CREST syndrome, can present as an isolated lesion.
- As in this case, calcinosis can be present without any renal or other systemic disease.
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