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 symptoms of 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:
- Alkali/acid elution: haemoglobin A+J (confirms the presence of abnormal haemoglobin J).
- Globin: fast beta chain variant (abnormal beta chain).
- Isoelectric focusing: haemoglobin A+J.
- Abnormal haemoglobin: 48% (a high percentage of haemoglobin J).
- Haemoglobin A2: 2.58% (normal <3%).
- Sickledex: 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 (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 levels. Current guidelines recommend HbA1c levels of less than 7% as a target for optimal chromatographic conditions. HbA1c can be measured chemically, chromatographically, and electrophoretically. Most autoanalysers use the chromatographic method. Haemoglobin variants may affect chromatographically measured HbA1c levels either by inducing an abnormal peak and thereby making the estimation of the fraction of HbA1c unreliable, or by reducing time available for glycation as a result of reduced red cell survival. These effects may coexist. Physicians should be aware of the potential pitfalls of HbA1c as a measure of long term diabetic control. Apparent discrepancies between glycaemic control reflected in day to day blood glucose concentrations, and HbA1c values should be noted. HbA1c levels are inappropriately affected by factors other than long term glycaemia as shown in boxes 1 and 2. Schnell et al reported a prevalence of abnormal haemoglobin variants of 0.6% among 15 000 HbA1c estimations in a period of over six years. In such individuals a method unaffected by abnormal haemoglobin variants, such as a turbidimetric inhibition immunoassay or alternate methods of chromatography should be used.

Final diagnosis
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 illustrated 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 discoloration 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, proximal and distal. 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 abductors. 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
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 gammopathy.

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, it mainly affects men, does not affect the upper limbs. Most patients have non-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 glycemic control had been poor for a factory 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 chills out 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 diseases that can cause proximal muscle weakness, and it may also be seen in myasthenia gravis. Acute myotonic dystrophy, and some connective tissue diseases, including hyperthyroidism, myxoedema, Cushings syndrome, acromegaly, osteomalacia, Addison’s disease, and primary hyperaldosteronism. These are seen in 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 ascertained 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 muscle unit poten-

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 myositis and malignancy, the temporal relationship being unclear. In some patients, pre-existing myositis recurs in patients with 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 in both men and women. 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 to be as high as 45% of polymyositis patients at the time of diagnosis. Intestinal lymphoma occurs in approximately 10% of polymyositis patients, at least half of which have Jo-1 antibodies. These are antinuclear antibodies associated with a more modest response to treatment and poorer prognosis and which are found in around 20% of patients with polymyositis. Other antibodies seen in polymyositis include antinuclear antibodies, seen in 16%–18% 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.

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 corticosteroid treatment in responders. Improvement in muscle strength occurs later, usually within 3–6 months. Once there has been a full response, a gradual reduction in corticosteroid therapy is often possible. Patients who do not respond to corticosteroids could be considered for other treat-
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.

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 changes 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 immunoglobulin 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 differential diagnosis of a painful proximal myopathy. The clinical, biochemical, electrophysiological, 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

Lumbar facet synovial cyst

Q1: What is a lumbar facet synovial cyst?

Lumbar facet synovial cyst was first described in 1968 by Kao et al. It is now being commonly reported with advanced neuroimaging techniques. It can pose serious diagnostic and therapeutic problems. The aetiology of this condition is degenerative including osteoarthritis, rheumatoid arthritis, and spondylolisthesis. It is commonly located at L4/5 in the most mobile part of the spine and is uncommon in cervical and thoracic regions. Repeated microtrauma is blamed for its aetiology. It is related to the degenerative facet joint. It might be a very common cause of refractory low back pain with radicular pain; it is very rarely bilateral. It can present, although very rarely, acutely as an emergency and there have been reports of cervical cord compression and cauda equina syndrome after a bleed into this cyst. Elderly patients with low back pain and radiation with a leading symptom of aggravation of pain on standing and walking should be suspected.

Q2: How is it diagnosed?

Blood tests and radiographs are usually unhelpful. MRI is the investigation of choice. The differential diagnosis with MRI could be unhelpful. MRI is the investigation of choice. Blood tests and radiographs are usually unhelpful. MRI is the investigation of choice. The differential diagnosis with MRI could be a migrated disc fragment, a perineural cyst, schwannoma, and a extradural space occupying lesion. Pathologists divide these cysts into synovial and ganglion types but they do not have any prognostic significance.

Q3: How is lumbar facet synovial cyst treated?

It is treated only if it is symptomatic. If it is an incidental finding, analgesia can be given. Spontaneous disappearance has been reported in 10% of these cysts. Aspiration has led to recurrence and steroid injection into the cyst has been reported to increase the severity of pain. Surgery is the treatment of choice with excision of the cyst and associated laminec- tomy. If there is associated instability then fusion is the treatment of choice.
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 sarcoidal type of tissue response or granulomas. Other possible entities are foreign body granuloma and osseous granulomatous disease as oral Cohen’s disease, granulomatous chelitis, and Melkerson’s syndrome. In this patient our clinical diagnosis was minor salivary gland tumour given the site of occurrence, hard nodular swelling with overlying normal mucosa.

Q2: How will you establish a definitive diagnosis and suggest their investigations necessary for the same?
Clinical features along with histological evidence of non-casating epithelioid granuloma from tissue biopsy can be supplemented by chest radiography, the presence of tuberculin sensitivity or non-caseating epithelioid granuloma composed of aggregates of epithelioid cells, scattered multinucleated giant cells, lymphocytes, plasma cells, and fibroblasts. Two other features often seen in the granuloma are lanced concretions composed of calcium and proteins, known as “asters”, and “asteroid bodies”. Although these two features are characteristic, they are not pathognomonic.

Q3: Discuss the prognosis and treatment of this lesion?
Overall, the prognosis of sarcoidosis is good. The drugs of choice are glucocorticoids as they have the therapeutic effect of this is not definitive and possible for the sarcoidal lesion to resolve. In a series of cases, including basal cell carcinoma with dystrophic calcification, subepidermal calcified nodule, pilonidal sinus, and trichobezoar, the incidence of calcinosis cutis was not significantly different from controls.

Learning points
- Primary intraoral sarcoidosis is of rare occurrence.
- Wide excision is diagnostic as well as therapeutic.
- In patients presenting with smooth, submucosal, firm masses of tongue a possibility of granulomatous lesions and infections should always be considered.

References

An unusual cause of a discharging sinus
Q1: What is the diagnosis?
Calcinosus cutis is characterised by the deposition of calcium salts in the subcutaneous tissues of the body. Metastatic calcifications can occur in the body in hyperparathyroidism and end stage renal disease. Calcifications can also occur in a variety of other clinical settings. The lesion can present as a mass and is amenable to FNAC. In cytological preparations, deposits of calcium salts can be both amorphous and refractile on Diff-Quik and Papanicolaou stain. However, the material may not be birefringent with these stains. Alesin red stain for calcium permits demonstration of the characteristic birefringence.

A group of extremely small bacteria capable of precipitating calcium salts implicated in the pathogenesis of urinary calculi and calcific atherosclerosis have been identified as the nanobacteria. The pathogenesis of calcinosus cutis and its significance in conjunction with a variety of unrelated scarring and pre-existing cutaneous entities are incompletely understood. In a series of cases, including basal cell carcinoma with dystrophic calcification, subepidermal calcified nodule, pilonidal sinus, and trichobezoar, the incidence of calcinosis cutis was not significantly different from controls.

References

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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.

Learning points
- Not every discharging sinus is due to infection or malignancy.
- Not all that appears radio-opaque 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.

References

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A bed bound patient

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