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:

- Alkali/acid elution: haemoglobin A + J (confirms 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%).
- Sickledex: negative (no evidence of sickle cells).
- Haptoglobins: 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 levels. Current guidelines recommend HbA1c levels of less than 7% as a target for satisfactory control. 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 two 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 immunoaassay or alternate methods of chromatography should be used.

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 influenced 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 peribulbar 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, 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 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 polyneuropathy (CIDP) is an immune mediated neuropathy characterised by a re-lapsing or progressive course. By definition, symptoms and signs of the neuropathy must be present for at least two months, which dis-tinguishes CIDP from Guillain–Barré syn-drome. 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 pre-dominate. Although the hyperreflexia 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 amylopathy (also known as diabetic lumbosacral radiculopathy), especially given the pain and the weakness of her quadriceps muscles and the absent knee reflexes. However, this typically affects the knee and does not affect the upper limbs. Most patients have non-insulin dependent diabetes mellitus and although commonly associated with peri-ods of poor glycemic control, the develop-ment of this neuropathy is often unrelated to glycose control or the duration of glucose intolerance. In this patient glycemic control had been satisfactory with a glycated haemo-globin (HbA1c) of 6.5%. In diabetic amylopathy, the neuropathy begins with severe pain in the back, hip or thigh, the pain typically changing as burning, knife-like, and ach-ing. On examination there is weakness of hip flexors and extensors, knee flexors and exten-sors, 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 endo-crinological causes of proximal myopathy, including hyperthyroidism, myxoedema, Cushings syndrome, acromegaly, osteomalacia, Addi-sons disease, and primary hyperaldoste-ronism. Those seen in metastatic disease, myxoedema, Cushings and Addisons’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 fatiguability 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 means of muscle biopsy. Electromyography is usually abnormal in polymyositis with the following features: increased insertional and spontaneous activ-ity 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 moder-ately weak muscle and preferably from a ten-
der area. The predominant histological fea-tures in polymyositis include necrosis in vari-ous sizes, scattered necrotic and regenerating fi-bres, and endomysial inflammation with invasion of non-necrotic muscle fibres. All of the invaded and some of the non-invaded muscle fibres may express major histocompat-iability complex class I antigen which is not normally present in the sarcolemma of muscle fibres. The endomysial inflammatory cells consist primarily of activated CD8+ alpha, beta T cells, and macrophages. Again, because this 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 myositis and malign-ancy, the temporal relationship being un-clear. In some patients, pre-existing myositis recurs in patients with a new diagnosis of malignancy and in patients with a relapse of malignancy, myositis has occurred de novo.1,2 Dermatomyositis is associated with under-laying 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. A large Swedish population based study the incidence of cancer in patients with dermato-myositis 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 malign-ancy, myositis with secondary congestive heart failure or conduction abnormalities occur in up to one third of patients with poly-myositis. Polyrhythms has been reported in as many as 45% of polymyositis patients at the time of diagnosis. Intestinal lung disease occurs in approximately 10% of polymyositis patients, at least half of whom have Jo-1 anti-bodies. 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 overall. Other antibodies seen in polymyositis include antinuclear antibodies, seen in 16%– 40% of cases, and antibodies against the signal recognition particle, found in 40% 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 7 days of commencement of treatment in responders. Improvement in muscle strength occurs later, usually within 3–6 months. Once there has been a full response the dose of steroid 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 or deterioration.

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 dermato-myositis and polymyositis.7 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 requires regular liver function testing. Bone densitometry may be performed to assess bone density and vitamin D supplementation is recommended. General supportive measures include good nutritional and medical care as well as physio-therapy 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. The chest X-ray should be performed every 6 months. Computed tomography or magnetic resonance imaging of the chest and abdomen and ultrasound of the liver should be performed every 6 months. A lung function profile should all be recorded. Urinalysis should be performed as well as chest radio-graphy. The chest X-ray should be performed every 6 months. Computed tomography or magnetic resonance imaging of the chest and abdomen and ultrasound of the liver should be performed every 6 months. A lung function profile should all be recorded. Ultrasound and/or magnetic resonance imaging of the liver and abdomen should be performed every 6 months. 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 evalua-tion.9

Discussion

Polymyositis is a non-suppurative inflamma-toxins condition of the muscles characterised by necrosis of the muscle fibres with evidence of regeneration and inflammation. Generally it presents in patients over the age of 20 years and it 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 dermato-myositis.
macrophages. than the endomysium, and the infiltrate is non-necrotic fibres is not prominent. In addi-
tion inclusion body myositis, invasion of present, in contrast to polymyositis and cal finding is of perifascicular atrophy. Al-
other clinical features listed above. T ypically dermatomyositis is not merely determined by
length of time before presentation. Our however it showed relatively little inflamma-
tish. On initial assessment by occupational therapy and physiotherapy, the patient re-
quired 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 moni-
toring 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, electro-
physiological, and pathological markers are typical of polymyositis and this patient dem-
strates the clinical response to therapeutic intervention that can be expected in this condition.

Final diagnosis
Polymyositis.

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References
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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 neuroim-
aging techniques. It can pose serious diagnos-
tic and therapeutic problems. The aetiology of this condition is degenerative including osteo-
arthritis, rheumatoid arthritis, and spondy-
olysisis. 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 actio-
pathogenesis. 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 cortical cord compression and cauda equina syndrome after a bleed into this cyst. Elderly patients with low back pain and radiation with a lead-
ing symptom of aggravation of pain on stand-
ing 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 a migrated disc fragment, a perineural cyst, schwannoma, and a extradural space occup-
ying lesion. Pathologists divide these cysts into synovial and ganglion types but they do not have any prognostic significance.
Q3: How is lumbar facent 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 re-
ported 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 lami-
nectomy. 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 reaction or granulomas. Other possible entities are foreign body granuloma and oro-facial granulomatosis known as Oral Crohn’s disease, granulomatous cheilitis, and Melkerson’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-casing epithelioid granuloma from tissue biopsy can be supplemented by chest radiography, the presence of tuberculin anergy, a positive Kveim-Siltzbach skin test, a raised serum angiotensin converting enzyme, and by an increased 24 hour urine calcium level. The characteristic histological picture of sarcoidosis in all involved tissues is the non-casing 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 laminated concretions composed of calcium and proteins, known as “Schaumann bodies” and satellite inclusions composed of calcium and proteins, known as “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 suppress the activated T helper-inducer cell and by an increased 24 hour urine calcium level. The prognosis of sarcoidosis is good.

References

A very unusual case of a discharging sinus

Q1: What is the diagnosis?
Calcinosi cutis
Calcinosi cutis is characterised by the deposition of calcium salts in the subcutaneous tissues of the body. Metastatic calcifications can occur in the body in hypocalcaemia, in 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. Alizarin red S 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 calcinosi 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, pilocytic, and nodular calcinosis, Mostre ultrastucturally examined the presence of Nanobacteria sp. All cases were negative for nanobacteria. Dystrophic calcification that occurs in conjunction with these entities does not likely involve a bacterial-induced aetiology. The cause of these entities remains unknown.

Subepidermal calcified nodule is a form of calcinosi cutis that most commonly occurs in children. The typical clinical presentation is of a solitary verrucous nodule on the face, but occasionally multiple. Smears usually show amorphous granular material consistent with calcium, and occasional histiocytes. The presence of amorphous calcium salts along with histiocytes in the appropriate clinical setting is diagnostic of calcinosi cutis. The diagnosis can be confirmed on histology.

Although this benign lesion can be suspected on radiological and clinical examination, FNAC and biopsy should always be done to rule out calcification in other potentially alarming conditions. Metastasis of this disorder has also been reported, though it is still benign.

Localised lesions can be injected with intralesional corticosteroids that may be beneficial due to the anti-inflammatory effect and inhibitory effect on fibroblast activity. Probenecid and colchicine have been beneficial in some individuals. In patients with hyperphosphataemia, magnesium or aluminium antacids may be effective due to phosphate binding ability. However, use in patients with renal insufficiency may result in magnesium or aluminium toxicity. Sodium edetate and diphosphonates may reduce bone turnover and inhibit the growth of ectopic hydroxyapatite crystals. However, prolonged treatment is necessary, and paradoxical hyperphosphataemia may result. There have been variably beneficial effects with the use of the calcium channel blocker diltiazem. The therapeutic effect of this is believed to be the antagonism of the calcium-sodium ion pump. Surgical excision can be undertaken when there is pain, recurrent infection, ulceration, or further growth. Even if treatment, though surgical trauma can stimulate calcification and recurrence is not uncommon.

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

References
Q2: What other features can be associated with the present clinico-radiological 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 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.

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