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 abnormally low 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%).
- Sickle: 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 glycedated 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, which is not a method unaffected by abnormal haemoglobinopathies, such as abnormal haemoglobin J.

Final diagnosis
Abnormal haemoglobin variant.

References

Box 1: Causes of high/low HbA1c levels

High
- Newly diagnosed diabetes mellitus.
- Uncontrolled diabetes mellitus.
- Non-diabetic hyperglycaemia: acromegaly, phaeochromocytoma, thyrotoxicosis, Cushings syndrome.
- Splenectomy.
- Alcoholism.

Low
- Haemolytic anaemia: congenital (for example, spherocytosis and elliptocytosis), haemoglobinopathies, acquired haemolytic anaemias—for example, drug induced (dapsone, methyldopa).
- Chronic blood loss.
- Chronic renal failure (variable).

Box 2: Abnormal haemoglobin variants and HbA1c

High HbA1c
- HbF
- HbE
- HbD
- HbJ Capetown
- Hb Raleigh

Low HbA1c
- HbS
- HbC
- HbJ
- HbG
- Hb Ramdan

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 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, 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. Irrespective, 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 gammonopathy.

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 quad-riceps 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 peri-ods of poor glycaemic control, the develop-ment of this neuropathy is often unrelated to glucose control or the duration of glucose intolerance. In this patient, however, the interval to a new diagnosis of diabetes mellitus has been over 25 years. The second possibility is that the patient has amyloidosis. This is often delayed when compared with der-matomyositis. There is no associated skin rash, the diagnosis of myositis and polymyositis was compared to the incidence of cancer in patients with dermato-myositis. A biopsy can be normal. Antibodies directed against myelin proteins are present in a small percentage of patients, and as many as 45% of polymyositis patients have non-insulin dependent diabetes mellitus which has been shown to be an effective therapy for drug resistant dermatomyositis and polymyositis. 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 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 relapsed weakness. Patients who do not respond to cortico-steroids could be considered for other treat-ment modalities such as intravenous immune globulin, which has shown to be an effective therapy for drug resistant dermatomyositis 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 should not be used in pregnancy. Patients with relapse of malignancy should continue at annual inter-val. 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 stool for faecal occult blood and gastrointestinal endoscopy may be indicated and women should undergo mam-mography, pelvic ultrasonography, and have their serum CA-125 levels assessed. 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.8

Discussion

Polymyositis is a non-suppurative inflamma-tory 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 is more prevalent in females. It may be 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 der-matomyositis.
Box 2: Learning points

- Polymyositis generally presents over the age of 20 years and is commoner in females.
- Presentation is with neck flexor and proximal limb weakness evolving over weeks or months.
- Dysphagia occurs in ~1/3 of patients due to oropharyngeal/oesophageal involvement.
- Jo-1 antibodies occur in ~20% of cases and are associated with a poorer prognosis.
- Risk of malignancy with polymyositis is less than dermatomyositis but higher than in the general population.
- Inflammation in polymyositis is endomyosal with invasion of non-necrotic fibres whereas in dermatomyositis it is perimysial with no involvement of non-necrotic fibres.
- Majority of patients respond favourably to immunosuppressive therapies but usually require lifelong treatment.

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 (33 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 conjunction with the physical examination. 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, electro-physiological, and pathological markers are typical of polymyositis and this patient demonstrated 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 a migrated disc fragment, a perineural cyst, schwannoma, and an 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 laminctomy. 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: 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 orofacial granulomatosis as oral Cohn’s disease, granulomatous chelitis, 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?
A: Clinical features along with histological evidence of non-caseating epithelioid granuloma from tissue biopsy can be supplemented by chest radiography, the presence of tuberculin sensitivity, anergy, a positive Kveim-Siltzbach skin test, a 24-hour urine calcium level, and ultrastructurally examined the presence of amorphous calcium hydroxyapatite crystals. However, primary intraoral sarcoidosis is known as “asteroid bodies”. Although these features were seen in the present case, the most common cervicalofacial manifestation, excluding ocularr and lacrimal gland involvement, appears to be asymptomatic swelling of the parotid gland or cervical nodes. Intraoral presentation is uncommon, and in most cases systemic sarcoidosis has been diagnosed before the oral manifestation becomes apparent. One study reported the presence of non-casing granulomas in 38%-58% of biopsies of normal appearing oral mucosa of patients with known sarcoidosis. Very few cases of tissue involvement have been reported. A bilateral hilar adenopathy is the hallmark of this disease and is also seen in lymphoma, tuberculosis, coccidioidomycosis, silicosis, and bronchogenic carcinoma. The presence of skin anergy is typical but not diagnostic. The Kveim-Siltzbach skin test yields sarcoidosis-like lesions in 70%-80% of patients, with fewer than 5% false positive results. Angiotensin converting enzyme is raised in the serum in approximately two thirds of patients but is also seen in asbestososis, silicosis, berylliosis, fungus infection, granulomatous hepatitis, hypersensitivity, pneumonitis, leprosy, lymphoma, and tuberculosis. A raised 24 hour urine calcium level is consistent with the diagnosis but is not specific.

Q3: Discuss the prognosis and treatment of this lesion?
A: Overall, the prognosis of sarcoidosis is good. The drugs of choice are glucocorticoids as they suppress the activated T helper-inducer cell processes occurring at the sites of the disease. Some advocate only surgical excision of the lesion, some medical treatment, while others combine the two modalities. Radiation also has been used as a mode of treatment, while spontaneous healing was documented in a few cases. Our patient responded well to the surgical treatment.

Discussion
Sarcoidosis is a disease that has highest occurrence in the third and fourth decades of life and exhibits a slight female predominance (1.5:1). In a young adult with constitutional complaints, respiratory symptoms, erythema nodosum, blurred vision, and presence of bilateral hilar lymphadenopathy, the diagnosis is almost always sarcoidosis. None of these features were seen in the present case. The most common cervicalofacial manifestation, excluding ocularr and lacrimal gland involvement, appears to be asymptomatic swelling of the parotid gland or cervical nodes. Intraoral presentation is uncommon, and in most cases systemic sarcoidosis has been diagnosed before the oral manifestation becomes apparent. One study reported the presence of non-casing granulomas in 38%-58% of biopsies of normal appearing oral mucosa of patients with known sarcoidosis. Very few cases of tissue involvement have been reported. A bilateral hilar adenopathy is the hallmark of this disease and is also seen in lymphoma, tuberculosis, coccidioidomycosis, silicosis, and bronchogenic carcinoma. The presence of skin anergy is typical but not diagnostic. The Kveim-Siltzbach skin test yields sarcoidosis-like lesions in 70%-80% of patients, with fewer than 5% false positive results. Angiotensin converting enzyme is raised in the serum in approximately two thirds of patients but is also seen in asbestososis, silicosis, berylliosis, fungus infection, granulomatous hepatitis, hypersensitivity, pneumonitis, leprosy, lymphoma, and tuberculosis. A raised 24 hour urine calcium level is consistent with the diagnosis but is not specific.

Final diagnosis
Primary intraoral sarcoidosis.

References

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