An interesting case of thirst and polyuria

Q1: What are the possible causes of thirst and polyuria in this woman?

The two likely causes of thirst and polyuria in this patient are central diabetes insipidus secondary to previous pituitary surgery and hypercalcaemia. In our patient, a normal water deprivation test excluded central diabetes insipidus.

Cranial surgery accounts for 20% cases of central diabetes insipidus in adults. After pituitary surgery, persistent polyuria develops only when the injury is sufficiently high in the supraoptico-hypophyseal tract to cause degeneration of the supraoptic and paraventricular nucleus. Thus although transient diabetes insipidus may follow any injury to the neurohypophysis, permanent cranial diabetes insipidus is uncommon after pituitary surgery.

Hypercalcaemia causes transient nephrogenic reverse osmotic diuresis, although indirect resorption may also occur. The manifestation of hypercalcaemia may be life threatening hypercalcaemia has been noted in 5% cases and none were due to primary hyperparathyroidism.

Serum calcium concentrations are generally less than 2.7 mmol/l, but they may rise to 10 mmol/l during illness and stress, dehydration, increase in bone turnover, or osmotic diuresis. PTH concentrations to normal, for which glucocorticoids and sodium haemoconcentration are a factor, but volume depletion is the primary factor in the increase in serum calcium concentration.

A common in secondary hypoadrenalism. Raised calcium binding proteins caused by hyperparathyroidism present the same problem as does thyrotoxicosis.

Hydroxylase activity increases serum 1,25-dihydroxycholecalciferol concentrations, particularly in individuals with decreased renal tubular reabsorption of calcium.

The diagnosis of primary hyperparathyroidism is generally straightforward. In 71% of cases, serum calcium is raised to 10.5 mmol/l or more.

The two likely causes of thirst and polyuria in this woman are central diabetes insipidus secondary to previous pituitary surgery and hypercalcaemia.

Q2: What are the possible causes of hypercalcaemia?

The possible causes of hypercalcaemia include thyrotoxicosis, relative glucocorticoid insufficiency during illness and stress, dehydration, acromegaly, and hyperparathyroidism as part of multiple endocrine neoplasia syndromes. Serum calcium concentration is raised in thyroid disease, and this is a feature of myxoedema. Serum calcium concentrations are generally less than 2.7 mmol/l, but life threatening hypercalcaemia has been described. Thyroid hormones absorb bone directly, although indirect resorption may also occur by activation of local factors such as interleukin-1 or by increasing sensitivity to circulating PTH. β-Adrenergic blocking agents can reverse the hypercalcaemia as can definitive therapy with carbimazole.

Hypercalcaemia is detected in 6% cases of primary adrenal insufficiency but is less common in secondary hypoadrenalism. Raised calcium binding proteins caused by haemococoncentration are a factor, but volume repletion with saline does not restore calcium concentrations to normal, for which glucocorticoid replacement is required.

Growth hormone stimulation of renal 1α-hydroxylase activity increases serum 1,25-dihydroxycholecalciferol concentrations reported very rarely in the literature and presented an unusual diagnostic challenge in this case, specially as she was on thyroxine replacement therapy after hypopituitarism.

Final diagnosis

Thyrotoxicosis due to Graves’ disease causing hypercalcaemia in a patient with hypopituitarism after treatment of acromegaly.

References


Q3: Discuss the clinical features and management of this lesion

Clinical features

The Merkel cell carcinoma is a rare but aggressive tumour presenting as a dark red to dark blue papule. It usually arises on the head, neck and the extremities of the elderly. It is often associated with other neoplasms, most commonly with a squamous cell carcinoma previously resected from the same anatomical site. The two may also coexist. It is also associated with Bowen’s disease and basal cell carcinoma.

The most important differential diagnosis is metastatic oat cell carcinoma as there are no specific histological differentiating features between the two. It is, therefore, important to undertake a careful history and examination followed by chest radiography to rule out a primary lung lesion.

Histology

The cellular pattern ranges from trabecular to an insular or to a diffuse growth but all may coexist in a single tumour. The lesion tends to occupy the whole of the dermis with sparing of epidermis by a thin zone of Grenz. Cytologically the cells are monomorphic with scanty cytoplasm and homogenous nuclei with central nucleoli (fig 1A).

Staining techniques

Silver stains are negative, indicating the small number of neurosecretory granules.

Immunohistochemistry

This is helpful in differentiating Merkel cell carcinoma from other tumours such as lymphoma, melanoma, and metastatic oat cell carcinoma.

The useful markers studies are:

- Positive for low molecular weight keratins such as AE1 or CAM 5.2, epithelial membrane antigen, neuron specific enolase (fig 1B), and chromogranin.

www.postgradmedj.com

A proliferating pimple

Q1: What is the differential diagnosis on clinical examination?

The possible differential diagnosis on clinical examination is:

- Dermatofibroma.
- Benign primary melanoma.
- Metastatic oat cell carcinoma.
- Angiosarcoma.

Q2: What does the histology reveal (see p 249) and what histological techniques are used to establish the diagnosis?

The histology reveals malignant round cells consistent with a Merkel cell carcinoma.

A rare primary endocrine tumour arising from Merkel cells.

History

The Merkel cell is a round cell in the basal layer of the epidermis named after Fredrick Sigmund Merkel who discovered it in 1875. These cells can be isolated or arranged in clusters around hair follicles, which are innervated and function as touch receptors. The tumour was first described by Tucker in 1972 who, along with Tang in 1978, described the intradermal lesion.

Q3: Discuss the clinical features and management of this lesion

Clinical features

The Merkel cell carcinoma is a rare but aggressive tumour presenting as a dark red to dark blue papule. It usually arises on the head, neck and the extremities of the elderly.

Histology

The cellular pattern ranges from trabecular to an insular or to a diffuse growth but all may coexist in a single tumour. The lesion tends to occupy the whole of the dermis with sparing of epidermis by a thin zone of Grenz. Cytologically the cells are monomorphic with scanty cytoplasm and homogenous nuclei with central nucleoli (fig 1A).
Merkel cell carcinoma.

reported to regress spontaneously. Some Merkel cell carcinomas have been

Management

• Negative for S-100 protein, carcinoembryonic antigen, and lymphocytic markers.

Some Merkel cell carcinomas have been reported to regress spontaneously. The optimal treatment is not well defined due to its rarity and the limitations of retrospective data. Early lesions can be managed by surgical resection alone. Mohs' microsurgery, which provides immediate histological assessment of resection margins, has a role in ensuring tumour clearance at the lateral and deep margins. It is not known whether prophylactic lymph node dissection and/or adjuvant radiotherapy increases the survival. Merkel cell carcinoma is a radiosensitive tumour and the field of treatment should include both the primary and the regional lymphatics. The role of chemotherapy is still controversial and should be considered in patients with advanced disease who are unfit for surgery.

Final diagnosis

Merkel cell carcinoma.

References


Figure 1  [A] Haematoxylin and eosin stain showing Merkel cells. Arrow shows a typical cell with a central nucleolus. [B] Merkel cells showing positive staining with neuron specific enolase.

An episodic eruption

Q1: What is the name given to this rash (see p 249), and how is the appearance described?

The rash is erythema gyratum repens. The specific features of this figurate rash are concentric erythematous arcs and rings, as well as serpiginous bands and stripes in alignment. The wholly pattern was initially described in 1953 by Gammel as ‘knotty cypress wood grain’. The rash spreads over the skin at a rate of about 1 cm a day, and may leave a similarly patterned scale in its wake. It is not raised, and is associated with pruritus (50%) and cosinophilia.

Q2: What underlying diseases does it suggest?

The rash is most commonly associated with internal malignancy. In one literature review of 49 cases the most common accompanying neoplasms were bronchial (32%), or were found in the oesophagus (8%) or breast (6%), or were unidentified metastatic malignancies (6%); less common were tumours of the pharynx, stomach, bowel and pancreas, as well as of the genitourinary tract. Lymphoreticular neoplasms were under-represented. In addition, the rash has been found in association with tuberculosis, limited systemic sclerosis (CREST syndrome), secondary Sjogren’s syndrome, virginal breast hypertrophy and hypercortisoldiabetic syndrome, although most of these are single case reports. In about 20% of cases, in whom follow up has continued for one to three years, there is no associated underlying disease.

Discussion

Erythema gyratum repens is one of several paraneoplastic eruptions which, while rare, are important for signifying the presence of internal malignancy. Such rashes often precede the clinical identification of an underlying tumour by months or years. Consequently, their discovery should prompt an extensive screen for occult malignancy which needs to be repeated regularly for at least several years, but possibly up to 5–10 years after the rash’s disappearance. Examples of some of these rashes are listed in table 1.

These rashes have in common the fact that they do not arise from malignant infiltration of the skin, or from local tumour pressure effects (for example, lymphoedema), but are the result of immune, metabolic or endocrine effects, that have been identified in only some cases.

In the case of erythema gyratum repens evidence exists for an immunological basis. Techniques employing immunohistochemistry have shown a B cell lymphocytic and eosinophilic infiltrate around dermal vessels, with an inconsistent presence of immunoglobulin and C3 deposits in either the basement membrane or epidermis. Theories for the rash’s aetiology include cross reaction of tumour antigens in association with specific human leucocyte antigen (HLA) haplotypes or immune complex deposition. Interestingly, the rash conforms in its spatiotemporal pattern to that seen in a chemical reaction diffusion model—the Belousov-Zhabotinski reaction—that describes other biological patterns, such as that found in slime mould.

Rashes with a paraneoplastic association may also occur in patients in whom no malignancy is ever found, despite extensive investigation and follow up. Moreover, such rashes have a tendency to co-occur: there are several reports of erythema gyratum repens coexisting with pemphigus, pemphigoid, ichthyosis, hyperkeratotic palms and soles, and poriiform lesions.

Erythema gyratum repens appears to persist in those cases where carcinoma is recognised, but it may resolve with steroid treatment in both patients with and without coincident malignancy. Dapsone has also been effective in a patient with hypercortisolism. In one case associated with Sjogren’s syndrome, secondary to rheumatoid arthritis, the rash appeared episodically, corresponding to adjustments (up and down) to the dose of prednisolone. Our patient’s dose of prednisolone remained constant throughout.

Course

The patient was screened for occult malignancy, but thorough clinical examination, an oesophagogastroduodenoscopy, barium enema, and computed tomography of the

Table 1 Paraneoplastic rashes, with the most common associations shown

<table>
<thead>
<tr>
<th>Rash</th>
<th>Common associated malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema gyratum repens</td>
<td>Bronchial carcinoma</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Bronchial carcinoma</td>
</tr>
<tr>
<td>Necrotic migratory erythema</td>
<td>Pancreatic duct carcinoma</td>
</tr>
<tr>
<td>Superficial migratory thrombophlebitis</td>
<td>Pancreatic glucagonoma</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Pancreatic glucagonoma (Trousseau’s sign)</td>
</tr>
<tr>
<td>Flushing</td>
<td>Gastrointestinal malignancy, especially gastric</td>
</tr>
<tr>
<td>Nodular panniculitis</td>
<td>Carcinoiand</td>
</tr>
<tr>
<td>Ichthyosis/pruritus</td>
<td>Pancreatic carcinoma</td>
</tr>
<tr>
<td>Other: Hypertrichosis lanuginosa, hyperhidrosis, hyperpigmentation, hyperkeratosis.</td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>


A 15 year old girl with fever, jaundice, haemolysis, and sudden clinical deterioration

Q1: What does the liver biopsy show (see p 250)?
A portal triad with marked oedema and fibrosis extending towards other portal triads is shown in fig 1A. Focal mononuclear cell infiltrates, ductular proliferation, and interface hepatitis are also visible. In fig 1B, hepatocyte ballooning and lytic necrosis are associated with feathery degeneration. These morphological findings are insufficient by themselves to establish a diagnosis since they are shared by a number of different liver diseases.

Q2: What is the most likely diagnosis?
The differential diagnosis in this case must include all the most important causes of fulminant hepatic failure, such as hepatitis A, B, C and D. Nevertheless, fulminant Wilson's disease should be considered the leading diagnosis. The three most relevant clues pointing to Wilson's disease are the age of the patient, the presence of Coombs negative haemolytic anaemia, and the low serum alkaline phosphatase level. Liver biopsy findings are compatible with Wilson's disease, since the vast majority of Wilson's disease patients have evidence of fibrosis, despite widely varying levels and patterns of hepatic inflammation and injury.

In other causes of fulminant hepatic failure, anaemia is not uncommon, and it is usually due to either bone marrow aplasia or coagulopathy and bleeding. Amanita phalloides releases a potent haemolysin, which, however, is not absorbed by the gastrointestinal tract and is not involved in the pathogenesis of signs and symptoms of the intoxication. An association between Budd-Chiari syndrome and haemolysis is reported only in patients where obstruction of the hepatic veins complicates paroxysmal nocturnal haemoglobinuria (a chronic disease). Haemolysis is one of the cardinal manifestations of HELLP syndrome, which is a late complication of pregnancy: being due to red cell membrane injury, in patients with HELLP syndrome a peripheral blood smear must show red blood cell fragments and/or free blood cells with a thorny or spiculated surface.

A further possibility to be considered is leptoisopsis, where haemolysis can contribute to anaemia, since exposure to environmental sources, in the present case, was possible or even likely. In Well's syndrome, however, haemolytic anaemia is invariably of the microangiopathic type.

Course
The attending physicians considered fulminant Wilson's disease and leptoisopsis, mainly in view of the history of exposure to rat excrement, the two most likely diagnoses. Direct and indirect methods of leptoisopsis detection, including a search for leptoisopsin DNA in the blood by polymerase chain reaction, were negative. The hepatic copper content was 600 µg/g dry weight (normal <50). The patient was listed for emergency liver transplantation, but she died of multiorgan failure 36 hours later before a suitable donor was found. Permission to perform a postmortem examination was denied.

The results of genetic testing, performed on a blood sample sent to a reference laboratory, were obtained only several weeks later, and showed a compound heterozygote genotype (His1069Gln; Val1262Phe).

Box 1: Main causes of fulminant hepatic failure

**Drugs and toxins**
- Acetaminophen.
- Halothane.
- Isoniazid.
- Valproate.
- Amanita phalloides.

**Infections**
- Viral hepatitis (A to E).
- Non-A to E hepatitis.

**Vascular diseases**
- Budd-Chiari syndrome.

**Metabolic diseases**
- Acute fatty liver of pregnancy.
- HELLP syndrome.
- Reye's syndrome.
- Wilson’s disease.

Discussion
Wilson's disease is a rare inborn error of metabolism (frequency between one in 30 000 and one in 100 000 live births), due to mutations in the recently discovered ATP7B gene. The Wilson's disease gene encodes for a P-type ATPase responsible for the transport of copper across cellular membranes, using ATP as an energy source. Dietary copper is absorbed in excess with respect to body requirements; since it is toxic, the generation of free radicals, in humans it is actively excreted via the hepatobiliary route. In the hepatocyte, the ATP7B protein has both a perinuclear location, where it is probably involved in delivering copper to apoprotein, and a plasma membrane location, where it may be responsible for the efflux of copper from the hepatocyte. Its function can be altered by a very large number of different disease specific mutations, including single base insertions and deletions, frame shifts and missense, non-sense, and splice site mutations (A continuously updated database can be freely downloaded at the web site of the University of Alberta.) Most patients are compound heterozygotes. As a result of any of these mutations, progressive copper accumulation occurs. The excess copper is bound to metallothionein and distributed evenly throughout the cytoplasm. When the binding capacity of metallothionein is exceeded, copper is partly deposited in lysosomes, leading to hepatic dysfunction. It also leaks out into the blood and is deposited in the brain and other tissues.

The most common initial clinical manifestations of Wilson's disease are those of chronic liver disease, fulminant hepatic failure, neurological disease, and haemolysis; affected relatives of a proband may be identified in a family. Wilson's disease is a late complication of pregnancy: being due to red cell membrane injury, in patients with HELLP syndrome a peripheral blood smear must show red blood cell fragments and/or free blood cells with a thorny or spiculated surface. This often occurs in young women with persistently high liver enzymes. In addition, the presence of splenomegaly and of Coombs negative haemolysis in an adult female is a good clue. However, in all cases the diagnosis of Wilson's disease is confirmed by serum ceruloplasmin concentration and urinary copper excretion, limited by both false negative and false positive results.

The fulminant mode of presentation, which, for unknown reasons, is more common in males, is not exchangeable with "mutations" and can represent a formidable challenge for the clinician. It occurs suddenly, without clear precipitating factors, and is almost invariably associated with haemolytic anaemia, as hepatocytic necrosis results in the massive release of copper ions into the circulation. Thus, signs include jaundice, haemoglobinuria, and renal failure; in this setting, diagnosis is a matter of extreme urgency, since, if the patient is not promptly considered for liver transplantation, prognosis is uniformly poor.

In patients with hepatic failure younger than 35 years, a high index of suspicion for fulminant Wilson's disease is needed. In addition, the presence of splenomegaly and of Coombs negative haemolysis favour Wilson's disease with respect to other causes of fulminant hepatic failure. By contrast, confirmatory tests for Wilson's disease (box 2) too often fail to add significant diagnostic information in this difficult setting. The value of biochemical tests, such as serum ceruloplasmin, serum copper concentration and urinary copper excretion, is limited by both false negative and false positive results.
examination, are absent at the time of presentation in the majority of fulminant cases. Liver histology may show micronodular cirrhosis, without specific features; immunohistochemical techniques for copper staining are notoriously of little diagnostic value. Indeed, in fulminant forms, even measurement of the hepatic copper content, that many would consider the golden standard for diagnosis of Wilson’s disease, may be below the diagnostic level, because of massive release of copper from necrotic hepatocytes. Due to the heterogeneity of the genetic defect, the time needed to perform genetic testing is usually too long to meet clinical needs, although it may be a feasible option in selected patients (for example, in subjects from Sardinia, where 85% of cases are due to only five mutations). For unclear reasons, serum alkaline phosphatase may be low (and sometimes unmeasurable) in fulminant Wilson’s disease: a ratio of alkaline phosphatase to total serum bilirubin of less than 2, in association with an aspartate aminotransferase to alanine aminotransferase ratio of greater than 4 has been considered suggestive of Wilsonian liver failure by some, but not by others.

As soon as a diagnosis of fulminant Wilson’s disease is contemplated, the patient should be promptly transferred to a hospital with an active liver transplantation programme. While awaiting for an organ, plasma exchange with fresh frozen plasma replacement should be instituted. This has been shown to be a more efficient method to remove copper from the circulation than haemodialysis, peritoneal dialysis, and haemofiltration, with net copper removal reaching up to 12 mg per session.

**Final diagnosis**

Fulminant Wilson’s disease.

References


**Box 2: Diagnostic tests for fulminant Wilson’s disease**

- Serum ceruloplasmin concentration.
- Serum copper concentration.
- Urinary copper excretion.
- Hepatic copper concentration.
- Alkaline phosphatase to bilirubin ratio.

**GL Inflammation and Disturbed Gut Function: The Challenge of New Concepts**

4–6 October 2002, Freiburg, Germany.

**Targets for Treatment of IBD**

6–8 October 2002, Freiburg, Germany.

**Disease Progression and Carcinogenesis in the Gastrointestinal Tract**

9–10 October 2002, Freiburg, Germany.

For further information on the above contact the Falk Foundation eV, Congress Division, Leinensweg 5, PO Box 6529, D-79041 Freiburg, Germany (tel: +49 761 15140, fax: +49 761 1514359, email: symposia@falk foundation.de).

---

**PostScript**

**DIARY**

**Obstetric Anaesthetists’ Association Annual meeting**

9–10 May 2002, Nottingham (East Midlands Conference Centre). For further information contact the OAA Secretariat, PO Box 3219, Barnes, London SW13 9XR, UK (tel: +44 (0)20 8741 1311, fax: +44 (0)20 8741 0611, email: registrations@oaa-anaes.ac.uk). For further information contact Dr Stephen Hicks, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK (tel: +44 (0)2476 523540, fax: +44 (0)2476 523701, email: s.j.hicks@warwick.ac.uk).

**Professional Updating in Epidemiology. Design of Vaccination Programmes: From Sero-Epidemiology to Cost-Effectiveness**

8–12 July 2002, University of Warwick, Coventry, UK. The course intends to develop understanding of the epidemiological principles of vaccine programme design, including serological surveys, parameter estimation, transmission dynamic models, and cost-effective analysis of different programmes. For further information contact Dr Stephen Hicks, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK (tel: +44 (0)2476 523540, fax: +44 (0)2476 523701, email: s.j.hicks@warwick.ac.uk).

**Falk Workshop: Bile Acids and Pregnancy**

2 June 2002, Freiburg, Germany.

**Falk Symposium**

**Exogenous Factors in Colonic Carcinogenesis**

2–3 May 2002, Würzburg, Germany.

**Bile Acids: From Genomics to Disease and Therapy**

30 May–1 June 2002, Freiburg, Germany.
An episodic eruption

Postgrad Med J 2002 78: 252-253
doi: 10.1136/pmj.78.918.252

Updated information and services can be found at:
http://pmj.bmj.com/content/78/918/252

These include:

References
This article cites 6 articles, 0 of which you can access for free at:
http://pmj.bmj.com/content/78/918/252#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/