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 diabetes insipidus and hyperthyroidism. Diabetes insipidus is commonly due to the absence of ADH on the basolateral membrane of the collecting duct epithelium, resulting in increased water excretion. Hyperthyroidism, in this instance, is likely Graves’ disease due to detectable TSH receptor antibody. Glucocorticoid replacement therapy is required.

Q2: What are the possible causes of hyperthyroidism?

Hyperthyroidism can be divided into exogenous (e.g., iodine ingestion, exogenous T3 or T4 administration) and endogenous (e.g., Graves’ disease, toxic multinodular goitre). Graves’ disease, which is an autoimmune disease, is the most common cause of hyperthyroidism. The diagnosis is confirmed by homogenously increased tracer uptake on ¹²³I thyroid uptake scan (fig 1; see p 248) and positive TSHRAb. TSHRAb binds to the thyroid stimulating hormone receptor, activates adenylyl cyclase, and increases thyroid hormone production and secretion. The TSHRAb in Graves’ disease is referred to as stimulating or agonist type TSHRAb, while various antibodies including a blocking TSHRAb may also be present. The presence of a blocking antibody may coincide with the stimulating antibody. TSHRAb are not detectable in the normal population. A total of 80% to 100% of untreated hyperthyroid patients with Graves’ disease have detectable TSHRAb with thyroid stimulating activity. "Technetium pertechnetate, like iodine, is actively concentrated by the thyroid gland, undergoes negligible organic binding, and diffuses out of the thyroid as the plasma concentration decreases. The short half life (six hours) and consequent low radiation makes it suitable for thyroid imaging. Thyroid scintigraphy is used in the evaluation of nodular thyroid disease, to differentiate hyperplastic thyroid tissue, and thyroiditis. It is not recommended in the evaluation of straightforward Graves’ disease. In our patient, a diffusely increased uptake (even though thyroxine replacement was stopped only seven days earlier) confirmed the diagnosis of autoimmune hyperthyroidism.

Q4: Is there an association between acromegaly and thyrotoxicosis?

Acromegaly is well known to be associated with goitre as a result of generalised oedema. In a series of 80 patients with acromegaly from an iodine deficient region, 71% had goitre compared with 35% in patients with prolactinomas. Goitres were more common in female acromegalic patients compared with males. Hyperthyroidism was noted in 5% cases and none were due to Graves’ disease. Graves’ disease in patients with active or previous acromegaly has been reported very rarely in the literature and presented an unusual diagnostic challenge in this case, specially as she was on thyroxine replacement therapy after hypophysectomy.

Final diagnosis

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

References


A proliferating pimple

Q1: What is the differential diagnosis on clinical examination?

The possible differential diagnosis on clinical examination is:

• Dermatofibroma.
• Pyogenic granuloma.
• Malignant melanoma.
• Metastatic oat cell carcinoma.
• Angioma.

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 or trabecular carcinoma. This is a rare primary neopodocrine 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 round cells may be isolated or arranged in clusters around hair follicles, which are innervated and function as touch receptors. The tumour was first described by Yokel in 1972 who, along with Tang in 1978, described the intracytoplasmic dense core granules similar to those seen in neuroendocrine cells.

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, or 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. The tumour has a high incidence of local recurrence (39%) and regional recurrence (46%). Distant metastasis occurs to bones, liver, and lung.

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 nucleus (fig 1A). They may show a moulding effect as seen in small cell carcinomas.

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.

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SELF ASSESSMENT ANSWERS

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Final diagnosis

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References

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. Moh’s 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”.

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 hypereosinophilic 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.

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 to its spatiotemporal pattern to that seen in a chemical reaction diffusion model—the Belousov-Zhabotinski reaction—that describes other biological patterns, such as those 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 porsieriform 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 hypereosinophilic syndrome. In the 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...
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. 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 polychromatophilic blood cells with a thorny or spiculated surface.

A further possibility to be considered is leptospirosis, 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 leptospirosis, mainly in view of the history of exposure to rat excrement, the two most likely diagnoses. Direct and indirect methods of leptospira DNA in the blood by the 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 organ could be 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).

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 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, copper is excreted by the generation of free radicals, in humans it is actively excreted via the hepato-biliary route. In the hepatocyte, the ATP7B protein has both a perinuclear location, where it is probably involved in delivering copper to apoprotein C-II, and a plasma membrane location, where it may be responsible for the efflux of copper from the hepatocyte.

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

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

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