Case report

An unusual bullous eruption: olanzapine induced pseudoporphyria

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SUMMARY

A 27-year-old man with a background of schizophrenia presented during the summer months with a 2-day history of a blistering eruption predominantly affecting his hands, forearms and face. He had not knowingly been exposed to any chemicals or toxins and was otherwise well. Clinical examination revealed multiple, large, tense blisters affecting the sun-exposed sites. Histology subsequently demonstrated subepidermal blisters with minimal inflammation and negative immunofluorescence. Porphyrin biochemistry including faecal, urinary and serum samples were unremarkable and thus a diagnosis of pseudoporphyria was reached. There were no obvious triggers, however, olanzapine (an atypical antipsychotic) had been commenced 2 months previously and was deemed to be the most likely cause. This is the first report of pseudoporphyria being associated with an atypical antipsychotic and highlights the importance of eliciting an accurate drug history by specifically enquiring about any recent medication changes that could account for the clinical presentation.

BACKGROUND

The differential diagnoses for a blistering cutaneous rash is broad and unfortunately the diagnosis can often be delayed.¹ However, an accurate history and clinical examination together with a basic understanding of skin histology and, where appropriate, porphyrin biochemistry, makes it much easier to arrive at an accurate diagnosis. The porphyrias are a group of disorders associated with a variety of clinical presentations² but are often poorly understood and it is hoped that this case report will provide the reader with a better understanding of these conditions. This particular case required input from general physicians, dermatology, histopathology, psychiatry and a biochemist with a specialist interest in porphyrias and ultimately highlights the importance of effective multi-disciplinary team work to provide the best possible outcome for the patient.

CASE PRESENTATION

A 27-year-old man with a background of schizophrenia presented with a 2-day history of photo-distributed blisters affecting his hands, forearms and face. There was no recent foreign travel and his medications included olanzapine (an atypical antipsychotic), procyclidine, propranolol and co-codamol. Olanzapine was started 2 months previously during an acute psychotic episode but there were no changes to any of his other

medications and there was no recent use of antibiotics or anti-inflammatory drugs. He had not knowingly been exposed to any chemicals or toxins and reported that he did not drink alcohol. There was no history of excessive sun exposure but he did present during the summer months. Similarly, there was no relevant family history and this was the first time he had experienced such symptoms. Physical examination revealed multiple, large, fragile bullae predominantly affecting the dorsal aspect of his forearms and hands with similar lesions on his forehead. There was no mucosal involvement and the rest of the clinical examination was unremarkable.

INVESTIGATIONS

Routine laboratory investigations demonstrated an elevated white cell count of $19.2 \times 10^9/L$ with a C reactive protein of 47 mg/L. Renal function and liver function tests were unremarkable. Plasma porphyrins, urinary porphyrin precursors (aminolaevulinic acid and porphobilinogen) and faecal total porphyrins were all normal. HIV, hepatitis B and C and antinuclear antibodies were also negative.

A punch biopsy was taken from the bulla on the dorsal aspect of the right hand and demonstrated a subepidermal blister with minimal inflammation (figure 1). Eosinophils and neutrophilic microabscesses were not seen. There was no thickening of blood vessels or the epidermal basement membrane. On direct immunofluorescence, there were no deposits of immunoglobulin G (IgG), immunoglobulin A (IgA) or C3. The features were of a pauci-inflammatory subepidermal blister with negative immunofluorescence.

Medical photography was taken and images can be seen in figure 2.

DIFFERENTIAL DIAGNOSIS

The list of differential diagnoses for a blistering eruption is broad, however, a thorough history and clinical examination combined with skin histology and, if indicated, appropriate porphyrin biochemistry, should allow for an accurate diagnosis to be made. In this particular case, the histology specifically demonstrated a subepidermal blister with a lack of inflammation and negative immunofluorescence which is suggestive of a bullous cutaneous porphyria. The differential for this includes porphyria cutanea tarda, variegate porphyria and pseudoporphyria, all of which are indistinguishable on histology. However, porphyria cutanea tarda by definition has abnormalities in porphyrin

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Figure 1 (A) Punch biopsy from the bullous lesion on the dorsal aspect of the right hand. (H&E x 20 demonstrating a paucity of inflammatory cells within the dermis.)

biochemistry. Characteristic findings are elevated urinary uroporphyrin and 7-carboxyl porphyrin excretion with normal porphyrin precursors (aminolevulinic acid and porphobilinogen), positive plasma porphyrin fluorescence emission scan with a peak at 615–620 nm and raised total faecal porphyrins, predominantly isocoproporphyrin and 7-carboxy-porphyrin fractions. Variegate porphyria also has a distinct pattern of porphyrin abnormalities and can cause potentially fatal acute porphyria attacks with severe abdominal pain and neuropsychiatric symptoms. Hence, normal porphyrin biochemistry together with the aforementioned histological findings makes pseudoporphyria the most likely diagnosis. It is worth noting that acute intermittent porphyria presents with neuropsychiatric and abdominal symptoms but no skin manifestations and therefore would not be a relevant differential diagnosis in this case.

Figure 2 (A) Bullous lesions affecting the hand and forearm. (B) and (C) Bullae on the forehead that have already burst spontaneously.

TREATMENT

The mainstay of treatment involves cessation of the offending agent and strict sun protection strategies, namely, broad spectrum high factor sunscreens and avoidance of sun exposure where possible. In this particular case, olanzapine was stopped abruptly after discussion with the mental health team and switched to lorazepam to be used when required because, at the time, the patient was not keen to go on a different antipsychotic.

OUTCOME AND FOLLOW-UP

This man was discharged with outpatient dermatology clinic follow-up but unfortunately did not attend and so the clinical course following discharge remains uncertain.

DISCUSSION

The porphyrias are a diverse group of rare metabolic disorders that result from altered activity of enzymes in the heme biosynthetic pathway. At least four porphyrias are associated with chronic bullous photosensitivity, the most common being porphyria cutanea tarda. Importantly, accurate biochemical diagnosis of the specific type of porphyria is essential for correct management.

Pseudoporphyria is a photo-distributed bullous condition with the histological and clinical features of bullous cutaneous porphyria but without the biochemical abnormalities in porphyrin metabolism.³ Pseudoporphyria can occur at any age with bullae and skin fragility affecting sun exposed sites, typically the face and dorsum of the hands. Well-recognised triggers include ultraviolet radiation, chronic renal failure/haemodialysis and certain medications. Culprit medications that have been implicated include non-steroidal anti-inflammatory drugs (commonly Naproxen), diuretics, antibiotics, tyrosine kinase inhibitors (imatinib and sunitinib) and the antifungal voriconazole.^{4 5} Treatment consists of cessation of offending agents and sun-protection but unfortunately, lesions can persist for years after discontinuation of the offending medication as demonstrated by a case series of 20 patients.⁶ In cases where cessation of the drug is extremely high risk or not possible, dose reduction would not be unreasonable given that with certain drugs such as imatinib, there is some evidence to suggest that the severity of pseudoporphyria is dose-dependent.⁷

Histological examination of bullous lesions associated with pseudoporphyria usually reveals a non-inflammatory subepidermal blister with negative immunofluorescence and scant perivascular lymphocytic infiltration. Importantly, it is this paucity of inflammation that raises the possibility of a porphyria/pseudoporphyria. In contrast, blisters associated with bullous pemphigoid are also sub-epidermal but tend to be eosinophil rich with positive immunofluorescence. It is worth noting that the blisters seen in bullous pemphigoid are not usually distributed in sun exposed sites but, importantly, they are in the cutaneous porphyrias. Epidermolysis bullosa acquisita also shows cell poor subepidermal blisters as does cell poor variant of bullous pemphigoid. Both these entities can be excluded by direct immunofluorescence which shows linear pattern of IgG along dermo-epidermal junction. Another helpful feature of porphyrias and pseudoporphyrias (when present) are cytol or 'caterpillar' bodies which are elongated eosinophilic structures, running parallel to the epidermis, containing laminin and type IV collagen.⁸ Periodic acid-Schiff positive thickening of basement membranes of dermal capillaries is also a useful clue. Both of these were however absent in the index case.

Given that this patient had the classical clinical and pathological features of bullous cutaneous porphyria but normal faecal, urine and serum porphyrin biochemical markers, a diagnosis of pseudoporphyria was made. The most likely trigger was felt to be the combination of sun exposure and olanzapine that had been started 2 months previously, as there were no other obvious risk factors or culprit medications. Plasma concentration of olanzapine was not measured, principally due to the initial delay in diagnosis, but may be worth considering in patients newly presenting with obvious features of pseudoporphyria as its plausible that supratherapeutic levels may increase the likelihood of any adverse drug reaction. To the best of our knowledge this is

the first reported case of pseudoporphyria being associated with an atypical antipsychotic.

Contributors ORJ: responsible for literature review, first draft write-up and co-ordinating revision of the manuscript between the other co-authors. MFS: provided expert management advice on the case and also performed part of the literature review in relation to the clinical/diagnostic aspects of the porphyrias. Proof read and made amendments to be included in the final submitted version. AB: provided the written information and comments in relation to the histological aspects of the porphyrias. Helped with appropriate figure selection. Proof read and made amendments to be included in the final version. PW: responsible for leading the project and having overarching responsibility. PW was also responsible for conception of the case report as well as revision of the final manuscript.

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Learning points

- ▶ Pseudoporphyria presents with the same histological and clinical features of bullous cutaneous porphyria but without the abnormalities of porphyrin metabolism.
- ▶ Recent medication changes should always be specifically asked as part of an accurate drug history.
- ▶ Well-recognised triggers include diuretics, antibiotics, non-steroidal anti-inflammatory drugs and some antifungals but this is the first report of its kind associated with an atypical antipsychotic.
- ▶ Pseudoporphyria is a diagnosis of exclusion. First line samples required to exclude a bullous cutaneous porphyria are: random urine for porphyrin quantitation and ethylenediaminetetraacetic acid (EDTA) blood for plasma fluorescence emission spectroscopy. If these tests are positive, further testing including faecal porphyrin analysis may be needed to confirm the type of porphyria.⁹

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