SSRI-induced severe adverse cutaneous reaction – a case report

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As selective serotonin re-uptake inhibitors (SSRIs) are commonly prescribed, less common side-effects such as severe adverse cutaneous drug reactions (ACDRs) can be seen more frequently than with less frequently prescribed antidepressants. Sertraline is among the better tolerated SSRIs. Here, we describe a case of a sertraline-induced severe ACDR in a patient with depressive symptoms and cognitive impairment. The selection of an appropriate antidepressant proved challenging. A review of recent literature on the clinical and temporal presentation of SSRI-induced ACDRs is presented with management strategies.

Selective serotonin re-uptake inhibitors (SSRIs) are recommended as first line in the pharmacological treatment of depressive episodes where appropriate (NICE, 2016).1 SSRIs are usually well tolerated with fewer cardiotoxic effects compared with other antidepressants. The most common side-effects of SSRIs include gastrointestinal effects, anxiety, headache, insomnia, movement disorders and sexual dysfunction. Hyponatraemia may occur more frequently in older people (approximately 1 in 200 older patients per year).2 Sertraline is generally well tolerated and there is good evidence for considering sertraline in older people and following myocardial infarction.3 Serotonin has several effects on the skin, including being pruritogenic, pro-inflammatory and pro-oedema. Adverse cutaneous drug reactions (ACDRs) due to SSRIs are usually mild, though life-threatening ACDRs may occur. Increasing age, female gender, African-American ethnicity, polypharmacy and serious illness can all increase the risk of ACDRs.4

Though less commonly cited, ACDRs can occur with SSRIs as a class effect due to the SSRI active ingredient. As ACDRs are less common, their management can present less familiar clinical scenarios to clinicians. The clinical and temporal presentations of SSRI-related ACDRs vary. Clinical descriptions are relatively infrequent in the medical literature despite SSRIs being commonly prescribed. Milder ACDRs include urticaria, pruritus and photosensitivity. Although the prevalence of SSRI-induced severe ACDRs is low, they are serious and potentially life-threatening if unrecognised or untreated. In addition, SSRI-induced ACDRs may be dose-independent and therefore can occur early in treatment.5 Severe skin complications associated with antidepressant use include the following: 1. Erythema multiforme (EM) 2. Stevens-Johnson syndrome (SJS) 3. Toxic epidermal necrolysis (TEN) (Lyell’s syndrome) 4. Acute generalised exanthematous pustulosis (AGEP) 5. Drug-induced hypersensitivity syndrome (DIHS)6

The first three syndromes above are considered to be three severities of the same syndrome.7 These severe skin conditions may result in prolonged hospitalisation, substantial disability, and even death.8 Erythema multiforme (EM) is characterised by erythema and oedema. Skin changes appear mainly on distal parts of upper and lower limbs, in mouth mucosa and genitourinary organs.6 Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening multi-organ syndromes. They are characterised by epidermis death, mucosa laceration and organ damage. The type I (toxic) reaction is dose related.6 The rarer type II (idiiosyncratic) reaction occurs in hypersensitive patients and is unpredictable.9 Patients may experience flu-like symptoms, measles-like papulo-pustular eruptions and within 2 to 14 days, EM, pain, fever and chills. Complications may occur in digestive, respiratory, urinary systems,10,11 Mortality rates are 5% for SJS and 35% for TEN.12,13 Acute generalised exanthematous pustulosis (AGEP) is a rare but severe ACDR. Pustular skin lesions filled with yellow fluid occur rapidly, excluding the palms, soles and usually mucous membranes. Fever and neutropenia occur. AGEP may last for one to two weeks.6
Case notes | SSRI adverse events

Early phase DIHS may present with limited systemic involvement. In 1996, DIHS with systemic involvement was named DRESS (drug reaction with eosinophilia and systemic symptoms) to decrease ambiguity in clinical practice. DRESS is a serious, potentially life-threatening condition.

For a DRESS diagnosis, five out of six of the following are required:
1. Maculopapular exanthema appearing after three weeks of drug therapy
2. Lymphadenopathy
3. Fever
4. Leukocytosis (> 10 × 10^9/L):
   - Atypical lymphocytosis,
   - Eosinophilia;
5. Hepatitis

DRESS can result from SSRIs and other medications, eg anticonvulsants.

In this case, we describe a man with depressive symptoms and cognitive impairment who developed an SSRI-induced severe ACDR with resultant clinical treatment complexities.

Case presentation
A 70-year-old man had an approximately four-year history of mild forgetfulness, particularly over the previous two years. Initial examples included his forgetting to pay for items in shops, leaving the car door open when parked and mistaking items. On one occasion he left cabin luggage on an airplane. He became mildly repetitive in conversation and occasionally dysnomic. Interestingly, there was no time or spatial disorientation. He was independent in activities of daily living apart from at times struggling to sequence making breakfast and very occasionally forgetting a medication. He had felt increasingly low in mood over two to three years, possibly longer, with irritability and intolerance, latterly, disliking his grandchildren’s presence. Diurnal mood variation, reduced energy, poor concentration and motivation and social avoidance were present. He frequently thought about death, being ‘obsessed with a fear of dying’ but he was not suicidal. Psychosis, anxiety and excess alcohol were excluded.

He had a difficult childhood and had suffered with depression over 20 years previously, being prescribed diazepam but no antidepressants. His grandmother suffered from dementia. Medical history included benign prostatic hypertrophy with nocturia and constipation. Prescribed medications were tolterodine, finasteride, atorvastatin and aspirin.

Geriatric Depression Scale score was 22/30; Addenbrooke’s Cognitive Examination-Revised (ACE-R) score was 89/100 with marks lost in memory, fluency and attention only. Low mood was more clinically prominent than cognitive decline and depressive symptoms could not be fully excluded pre-cognitive decline. Blood tests, including B12, folate and thyroid tests were normal. A CT head scan was requested. A moderate depressive episode was considered with mild cognitive impairment possibly secondary to the affective change. Sertraline 50mg daily was commenced and tolterodine was substituted to minimise cognitive side-effects.

Adverse reaction
After three weeks of sertraline 50mg daily, there were positive effects on mood and irritability. CT head revealed global involution with no medial temporal lobe or other pathology. The patient then developed a whole-body puritic rash with worsening discrete red maculopapular lesions. He attended A&E on the day before his scheduled appointment, had blood tests taken and was prescribed antihistamines with no cause identified. Mild eosinophilia was noted. In the psychiatric clinic, sertraline was stopped due to possible DIHS. Two weeks later, his rash significantly worsened with a feeling of being generally unwell and a severe itch. At an urgent dermatology review, a lichenoid DIHS was diagnosed, secondary to sertraline. DRESS was noted as a potential risk had sertraline not been stopped. The rash continued to worsen even after sertraline cessation. Symptomatic treatment was advised with antihistamines and topical corticosteroid cream. Finally, after several weeks, the reaction began to resolve though low mood, irritability and negative cognitions resurfaced. As SSRIs had been the patient’s antidepressant preference, consultant dermatologist advice was sought about alternatives. The dermatologist advised that this reaction was due to the active drug rather than a manufacturing additive. SSRI treatment was inadvisable as, with a class reaction, further DIHS may be worse and possibly even lead to DRESS.

Five weeks later, his rash had fully resolved. He had low mood with marked irritability. He declined mirtazapine due to possible sedation and weight gain. Tricyclic-related antidepressants were excluded due to bladder outflow problems. Interestingly, the dermatologist also suggested that serotonin-norepinephrine re-uptake inhibitor (SNRI)
treatment would be too risky due to potential pharmacological similarities to SSRIs. Suitable antidepressant therapy was proving challenging.

Cognitive and functional problems had gradually declined. Affective problems secondary to prodromal Alzheimer’s dementia were later discussed as part of a differential diagnosis. Donepezil was subsequently titrated to 10mg daily. Following this, both he and his wife reported a reduction in his irritability. Three months later he felt that donepezil relieved constipation and indirectly his bladder outflow problems. This improved his sleep. His mood symptoms improved. His wife reported that he was now enjoying his grandchildren’s company.

Discussion
This case described an unusual, severe cutaneous reaction to sertraline. It was an early phase DIHS. The increasingly extensive use of SSRIs will probably increase the number of cases of cutaneous reactions due to these drugs. Clinicians need to be able to identify and prioritise possible ACDRs due to the frequency of prescribed SSRIs. This is particularly the case with severe skin reactions, which may be fatal. In addition, these reactions may occur with other antidepressants such as mirtazapine, SNRIs and trazodone as described in the literature. In this case, the patient had risk factors of advancing age, physical comorbidity and concomitant medications.

Interesting case reports have described more severe SSRl-induced ACDRs. SSRI-induced DRESS has been reported with citalopram and fluoxetine. A man developed extensive papular and purpuric erythema with keratinocyte necrosis and vasculitis in the citalopram case. EM and SJS have been described with sertraline. A 77-year-old man with AGEp six days after sertraline administration presented with very severe mucous membrane inflammation. Interestingly, the skin lesions were significantly intensified on sun-exposed areas. Cutaneous lesions remained for several weeks. Significant cutaneous paroxetine-induced vasculitis has also been reported. A recent paper described 11 patients with SSRI-induced maculopapular rash. Most reactions occurred a few days after SSRI initiation. The authors concluded that the increasing use of SSRIs may result in an increase in ACDRs and clinicians should be alert to these reactions. These cases clearly caused significant symptoms and if not managed appropriately, could have let to serious complications, eg DRESS.

Choosing an alternative antidepressant can be more challenging when comorbid physical conditions hinder alternative antidepressant choice, particularly in older people. The index and latter cases prompt the question as to whether an alternative SSRI can be safely considered when an ACDR occurs with an SSRI. One paper suggested that patients who discontinue one SSRI because of side effects can be treated successfully with another. However, a review of SSRI-induced ACDRs concluded that an index of suspicion is warranted for patients who develop a skin rash during treatment with an SSRI. Cases included a patient initiated on paroxetine who developed a pruritic, generalised rash with facial involvement. A similar reaction occurred with fluoxetine, suggesting a drug class effect. Other cases support this view. A patient developed a maculopapular, erythematous, pruritic rash in the third week with sertraline 50mg daily. This was similar to the index case here. Ten days following sertraline discontinuation and resolution, paroxetine 12.5mg daily caused a similar skin reaction by day 4. A further paper described two interesting cases. A 38-year-old woman developed an ACDR after eight days of fluoxetine treatment which subsided with fluoxetine cessation. Two months later, paroxetine caused the same ACDR. A 40-year-old man had several antidepressant prescriptions over one year – fluoxetine, fluvoxamine, paroxetine and sertraline – and each time a similar ACDR appeared. A case described an unpleasant itching rash with fluoxetine treatment rapidly recurring with sertraline initiation.

The author suggested that some individuals may be very sensitive to serotonin concentration increases. We suggest that the SSRI class should be avoided after an SSRI ACDR, especially if severe. This is due to the class effect and cross-reactivity which may occur at next exposure to the same antidepressant class.

Management
Management can be divided into pre- and post-treatment. Pre-treatment strategies include identification of those at risk, prescribing within guidelines to lowest effective doses and avoiding polypharmacy. Important post-treatment considerations include education, advice on limiting sun exposure if appropriate, early recognition and monitoring of an ACDR. Specifically, if an ACDR occurs in an outpatient setting, the offending SSRI should be discontinued. Early discontinuation of the suspected drug, especially if it has a short half-life, is associated with an improved prognosis (up to five-fold reduction in mortality). If required, at a later time, an antidepressant from another class can be
substituted. The case evidence presented suggests that alternative SSRIs could cause a similar or worse ACDR despite having different chemical structures. Treatment of the ACDR should be symptomatic (eg anti-pruritics, topical steroids) if the patient shows no signs of systemic reaction. The patient’s GP should be informed for their information and drug reaction documentation. If more severe signs are present, a senior dermatologist consultation should be obtained. We suggest immediate dermatologist consultation in the severest cases. This may be required even after discontinuation. Patients with more severe ACDRs (eg TEN) may need prompt hospitalisation. An alternative class of antidepressant to SSRIs (and possibly even to SNRIs) should be considered if there has been an ACDR to an SSRI.

Conclusion
Although ACDRs to SSRIs such as sertraline are relatively infrequent, given the high number of patients prescribed SSRIs, these reactions will be seen in practice. Knowledge of ACDRs is important because TEN and SJS have been reported, which are severe and may be life threatening. Management consists of pre- and post-treatment considerations. SSRI cessation and symptomatic treatment is appropriate for milder cases. In severe cases, dermatologist consultation is advised. Alternative antidepressants to SSRIs should be considered after an SSRI ACDR. This case highlights the need for good evidence-based clinical guidance on SSRI ACDRs and their management as these can be serious and life threatening. It is likely that clinicians may need to manage a case in clinical practice. Clinicians, even those less experienced, may encounter such cases due to the idiosyncratic, unpredictable nature of some ACDRs in hypersensitive patients.

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Declaration of interests
No conflicts of interest were declared.

References