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Correspondence

Urticaria in patients with diabetes: Adverse drug reaction or relapse of underlying autoimmune urticaria?

Sir,

Urticaria is a skin condition that presents with red, raised itchy lumps and disappear in a few hours only to re-appear, and sometimes with swelling attacks (angioedema). In a study on adverse drug reactions (ADRs) in patients with diabetes up to 15 per cent of ADRs were shown to be related to skin and appendages[1]. Autoimmune conditions such as thyroid disease and type 1 diabetes are factors that increase the odds of having urticaria[2]; and hence, it is believed that almost 45 per cent of patients with urticaria have autoimmune chronic urticaria (CU) and the rest are truly idiopathic CU[3]. A large population study reported that the odds of having urticaria in diabetes was 7.703 (12,778 patients with CU and 10,714 controls) with females higher than males[2]. The introduction of two new anti-diabetes drugs sodium glucose co-transporter-2 inhibitor (SGLT2-I) and dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) in patients may require closer follow up as studies have shown severe adverse skin events (81 reports, 7% of the skin cases) mainly occurring in females aged 18-65 yr who used SGLT2-Is as single anti-diabetic regimen[4-6].

This retrospective case note-based study was done in the department of Allergy and Immunology, Apollo Gleneagles Hospitals, Kolkata, India, to see the number of CU patient referrals with underlying diabetes, and whether any new diabetic medications were thought to have worsened or triggered urticaria in any of the patients. Ethical approval was obtained for this study from the Hospital Ethics Committee (IEC/2017/08/27), with written informed consent obtained as part of a larger study. Of the 1220 patients with acute urticaria (lasting less than 6 wk) who attended the Allergy and Immunology clinic during 2014-2016, 159 patients were diagnosed with diabetes (13% of referrals). There were 61 males and 98 females (female:male ratio of 1.60:1) with an average age of 38.2±12.5 yr (age range 25-90, median 36 yr). Case records revealed that 35 patients (22%) had uncontrolled diabetes requiring insulin at various time points. Seventy five patients were referred with a history of suspected ADRs (Table). Two patients (females aged 48 and 62 yr) developed severe urticaria within two weeks of starting SGLT2-I as a sole therapeutic agent, both of whom required immediate stoppage of the medication. Two other patients developed variable skin rashes after DPP-4 inhibitor (50 mg once daily) was added to metformin (1 g twice daily). These patients continued to develop rashes for nearly two weeks until a possible drug trigger was considered. It took between three and four months to control the urticaria after stoppage of the DPP-4 inhibitor. Twenty two patients gave a history of urticarial eruptions with use of non-steroidal anti-inflammatory drugs (aspirin included in 1 patient), four due to possible antibiotic use (but negative on specific IgE and challenge tests), three with severe angioedema due to angiotensin-converting enzyme - inhibitors with urticarial weals at different times and one with the use of hydrochlorothiazide. In 41 patients (55%) who developed urticaria, the suspected ADRs could not be confirmed (Table).

Investigations into underlying infection/metabolic/autoimmune causes of urticaria revealed 34 patients (21%) with autoimmune thyroid disease (positive anti-thyroid peroxidase or anti-thyroglobulin antibodies) with abnormal thyroid-stimulating hormone values (<0.03-67.4 mIU/l). Both hypo- and hyperthyroidism can be a cause of difficult urticaria and a subset of patients with chronic idiopathic urticaria may show autoantibody-associated urticaria (thyroid autoantibodies and IgE receptor autoantibodies)[7]. There were four patients with CU and hyperuricemia. Though the link with raised uric acid levels and CU remains unclear, it is perhaps an important factor in

Table. Description of patients with diabetes and urticaria (n=159)

Clinical characteristics	Number of patients (%)
Uncontrolled diabetes	35 (22)
Age (yr)	
Mean age±SD	38.2±12.5
Sex	
Males	61
Females	98
Female: male ratio	1.6
Anti-TPO/TG antibody positivity	34 (21)
Suspected ADRs	75
Confirmed ADRs	34 (45)
NSAID	22
ACE-I	3
Antibiotics	4
SGLT2 inhibitor	2
DDP-4 inhibitor	2
HCTZ	1
ADR unconfirmed	41 (55)
Hyperuricemia	4
Infections	6
Staphylococcal infection	3
Fungal infection (bladder)	1
Escherichia coli UTI	1
Ascaris lumbricoides ova (stool)	1
Skin test positive (to house dust mite)	7 of 20 (35)
Vitamin D deficiency <20 ng/ml	4 of 15 (29)
ANA positivity	5 of 18 (28)

TG, thyroglobulin; TPO, thyroperoxidase; ADR, adverse drug reactions; SGLT2, sodium glucose co-transporter-2 inhibitor; UTI, urinary tract infection; ANA, antinuclear antibody; DDP-4, dipeptidyl peptidase-4; NSAID, Non-steroidal anti-inflammatory drugs; HCTZ, hydrochlorthiazide, ACE-I, antiotensin converting enzyme-Inhibitor

the inflammatory response (the activation of NLRP3 inflammasome), and as an endogenous host 'danger signal' that needs further research[8]. Six patients had underlying infections when they presented with severe urticaria (3 patients with severe staphylococcal skin infections due to uncontrolled diabetes with HbA_{1c} >10% in all patients; one with fungal infection in urinary bladder; one with *Escherichia coli* urinary sepsis and one with *Ascaris lumbricoides* ova on stool examination).

The treatment of urticaria was followed according to standard guidelines[7], with most patients requiring high doses of antihistamines in various combinations (fexofenadine, hydroxyzine and cetirizine up to 10 mg three times daily). In almost all patients, the urticaria was not controlled when drug dosages were lowered but six weeks after the suspected drug was discontinued, use of high-dose anti-histamines and strict control of blood sugar. Only two patients required immunomodulation with cyclosporin for three months (100 mg twice daily for 6 wk then once daily for 6 wk) to control the urticaria (both also had autoimmune hypothyroidism).

In conclusion, this study showed that urticaria was common in patients with diabetes and that skin-related adverse events of the newer anti-diabetic drugs such as SGLT2-I and DPP-4 inhibitors might also pose a problem to patients. This needs to be studied in future.

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