A 14-year-old female patient came with the complaints of high-grade fever and cough for 5 days and rash over the body of 2 days duration. Fever was high grade, intermittent, not associated with chills, and decreased on medication. Rash consisted of itchy urticarial wheals all over the body that did not stay in one place for more than 24 h. This was also associated with mild swelling of the lip. The patient had presented to a general physician who prescribed tab cefpodoxime 200 mg BID and paracetamol for the fever after which she developed these lesions.

On examination, the patient was febrile (temperature – 100°F) with pulse rate of 94 beats/min and blood pressure of 100/70 mm of Hg. The patient had rhinorrhea. She also had conjunctival congestion. Skin examination showed multiple urticarial wheals present over the trunk, arm, back, face, and legs [Figures 1 and 2] as well as over both the palms. There was a mild swelling of the lips. There was no significant lymphadenopathy. Investigations showed a normal total leukocyte count with a raised serum IgE level of 642 IU/L (normal level <150 IU/L).

Based on the clinical features and temporal correlation of the medications to the urticarial rash, the patient was thought to be a case of drug-induced urticaria likely to be induced by cefpodoxime. Cefpodoxime was stopped immediately and the patient was put on clarithromycin. She was started on fexofenadine 180 mg OD for 3 days, following which the patient had improved dramatically.

**QUESTIONS**

- Why the diagnosis of drug-induced urticaria was made in this case?
- What are the other causes of urticaria in children apart from drugs?
- How will you differentiate between drug-induced urticaria and infection-induced urticaria?
- As this patient requires another antibiotic, what drug substitution should be done?
- What are the various mechanisms of drug-induced urticaria?
- Are there any reliable diagnostic tests for identifying drug allergen responsible for causing urticaria?
ANSWERS

Why the diagnosis of drug-induced urticaria was made in this case?

Two days after starting cefpodoxime, the patient developed a severe itchy urticarial rash with mild swelling of the lower lip. These wheals were evanescent in nature and lasted for <24 h.

Temporal relationship between the start of drug and the onset of symptoms and subsidence of urticarial rash following drug withdrawal is the most important indicator of its causality. Previous reports of adverse cutaneous reactions due to suspected drug in the literature help in making causality assessment. Beta-lactam antibiotics such as penicillins have been stated to be the most common cause of drug-induced urticaria.[1,2] Based on the application of Naranjo’s algorithm used for causality assessment, cephalosporins are more likely to have induced urticaria in this patient as compared to paracetamol. Successful dechallenge and previous reports of cephalosporin-induced urticaria are pointers toward cephalosporins as the cause of urticaria.

Why urticaria in this patient is not of infective origin? how will you differentiate between drug-induced urticaria and infection-induced urticaria?

Cephalosporins are frequently prescribed for infectious diseases such as sinusitis, URTI, and pneumonia. Infections can themselves precipitate urticaria. Although it is difficult to differentiate between the two, careful history, proper examination, and most importantly, clinical experience of a physician are helpful in such cases. In our patient, URTI was present. However, urticaria started resolving after drug discontinuation while viral infection continued to persist. Hence, in this case, fever and conjunctival congestion started before starting cefpodoxime and urticarial rash involving palms and soles started after talking cephalosporin. Hence, it can be assumed that the fever was infective in origin and the rash was drug induced. However, there is no definite diagnostic test to differentiate between infection-induced urticaria and drug-induced urticaria.

If this patient requires antibiotic, what drug substitution should be done in this case?

Drug-induced urticaria has been reported with several classes of antibiotics including penicillins, cephalosporins, aminoglycosides, tetracyclines, and sulphonamides, besides many others. Penicillins are the most common cause of drug-induced urticaria.[1] Patients with allergy to penicillin are more likely to have allergic reaction to cephalosporins than those who do not.[2] Cross-reactivity is more common with the first-generation cephalosporins than second- or third-generation cephalosporins. Hence, safer alternatives include azithromycin, clarithromycin, aztreonam, clindamycin, and linezolid. This patient was prescribed clarithromycin. As most viral infections are self-limiting, substitute antibiotics may not be required. However, it should be noted that antibiotics are sometimes prescribed to treat secondary bacterial infection in cases of viral URTI.

What are the various mechanisms of drug-induced urticaria?

Immunologically mediated drug-induced urticaria is a type I hypersensitivity reaction and requires a prior sensitization. Usually, the first course of the drug is uneventful. During the second exposure, the reaction develops within 24–36 h. On re-exposure, reaction may develop in minutes to an hour. This type of reaction can be severe and may be associated with anaphylaxis or angioedema.

Nonimmunologically mediated drug-induced urticaria is a drug reaction that resembles immediate hypersensitivity reaction, but does not have a sensitization phase. Usually, 50% of the reactions occur in the first 6–7 h.[3] The most common cause of nonimmune drug-induced urticaria is due to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Proposed mechanism for the same is overproduction of leukotrienes following the inhibition of constitutive COX-1 pathway. NSAIDs have known to aggravate chronic urticaria. Selective COX-2 inhibitors are much better tolerated, but they too have been shown to aggravate chronic urticaria. Paracetamol has been used extensively for aspirin-sensitive urticaria, but there have been a few reports of anaphylaxis due to acetaminophen.[4] Narcotic analgesics such as codeine and tramadol have also been implicated. Tramadol may also precipitate urticaria in patients who are sensitive to NSAIDs, hence may not be necessarily safe.[5]

Urticaria and angioedema due to angiotensin-converting enzyme (ACE) inhibitors are well known. This is due to decreased degradation of bradykinin due to the blockage of ACE. Since this is due to the basic mechanism, this is seen with all members of the class. This problem is not seen in angiotensin receptor blockers or ARBs as they directly block angiotensin receptor. However, one systemic review showed that angioedema may persist in up to 10% after switch from ACE-1 inhibitors to ARBs.[6] Vaccines have been cited as the third most common cause of drug-induced urticaria.[7] Acute or chronic urticaria has been shown to start within days to weeks following vaccination.
How drug-induced urticaria can be prevented in future?
Once it is confirmed that patient has drug-induced urticaria due to specific drug(s), the patient should be counseled and educated about it. He/she should be told that such episode may recur in future with intake of offending drugs. Drug allergy card should be given to patient mentioning offending drugs. Patients should be instructed to show this card to doctors if they are required to take medications for any ailment. In country like ours, medications are sometimes taken from pharmacists who may be unaware of clinical details or drug history of the patient. Chances of drug reaction may increase due to this. Drug list should be kept as minimum as possible and essentiality of drugs should be discussed with the clinician treating the patient, particularly who is taking multiple drugs.

Are there any reliable diagnostic tests for identifying beta-lactam antibiotics as the cause of drug-induced urticaria?
Detection of specific drug causing urticaria is the most important aspect of effective management. Various tests are claimed to be useful for detecting specific drug causing urticaria. They include intradermal skin tests, basophil activation test, fluoroenzyme immunoassay (FEIA), and radioimmunoassay (RIA). While drug provocation tests such as intradermal tests (IDTs) and skin prick test are more popular with beta-lactam antibiotics such as penicillin, they are found to be less useful for detecting cephalosporin hypersensitivity as exact allergenic determinants of cephalosporins are not known. Cephalosporins degrade to form heterogeneous reactive antigenic determinants which are yet to be known. Similarly, IDTs can be done only when drug or allergen is available in injectable or in solution form. In a study by Yoon et al., even when IDT with cephalosporins was positive, test-positive patients did not show immediate hypersensitivity reactions. While doing IDT, drugs such as cephalosporins tend to produce nonspecific irritant skin reactions resulting in false-positive reactions. Hence, the optimum concentration of cephalosporins that does not result in irritant reactions should be chosen. However, there is no consensus regarding this. ENDA/EAACI Drug Allergy Interest Group recommended a concentration of 2 mg/ml for cephalosporin skin tests. Several other studies indicated a concentration up to 20 mg/ml of cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefazolin, cephalexin, cefaclor, and ceftriaxone that do not produce irritant reactions and increases the chances of detecting drug hypersensitivity.

Actual application of BAT in clinical practice in cases of drug hypersensitivity has been limited to a few drugs such as beta-lactams, neuromuscular blocking agents, NSAIDs, or radiocontrast media. Data about the clinical experience of BAT are limited.

The specificity of FEIA ranged from 83.3% to 100% and sensitivity from 0% to 25% whereas the specificity of RAST was between 66.7% and 83.3% and sensitivity between 42.9% and 75%. Their study suggested that owing to high specificity, serum-specific IgE assays may be more useful than a drug provocation test in the patients with a history of beta-lactam anaphylaxis and negative skin tests.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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