Case report

Case of relapsing sulfasalazine-induced hypersensitivity syndrome upon re-exposure

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SUMMARY

Sulfasalazine-induced hypersensitivity syndrome (SIHS) is a serious systemic delayed adverse drug reaction that is associated with significant morbidity and mortality. Here, we report the first case, to our knowledge, of a patient with previously unidentified SIHS who developed a significantly more rapid and extreme recurrence on re-exposure to sulfasalazine. The patient is a 58-year-old woman with asymptomatic Crohn's disease who, 10 days after initiating sulfasalazine, developed fevers, diffuse rash, pancytopenia, hypotension and hepatitis without a definitive source of infection. Sixteen days after her first hospitalisation, she was restarted on sulfasalazine and was readmitted within 10 hours with a similar but more serious presentation, requiring vasopressors. She did recover completely without any further recurrence to date, after definitively discontinuing sulfasalazine. This case demonstrates the importance of recognising SIHS early in patients to prevent re-exposure to sulfasalazine and to ensure timely initiation of appropriate treatment.

BACKGROUND

Sulfasalazine is an immune-modulating medication that is used in the treatment of various autoimmune diseases. While it is generally well tolerated, sulfasalazine has been known to cause sulfasalazine-induced hypersensitivity syndrome (SIHS)[1 2]—a drug-specific version of the syndrome also known as drug reaction with eosinophilia and systemic symptoms (DRESS). SIHS is a systemic adverse drug reaction that typically manifests between 2 and 6 weeks after initiation of the drug and can be fatal.[3 4] DRESS (Including SIHS) often manifests with fever, rash, lymphadenopathy, hepatitis and blood dyscrasias (which may or may not include eosinophilia).[5 6] It has also been known to cause pneumonitis, myocarditis, nephritis, acalculous cholangitis and more.[7 8]

Despite the significant amount of data on SIHS, the timeline of relapse of SIHS on re-exposure to sulfasalazine has not been well described. Here, we report the first case, to our knowledge, of a patient with previously unidentified SIHS who developed a significantly more rapid and extreme recurrence on re-exposure to sulfasalazine.

CASE PRESENTATION

A 58-year-old woman was diagnosed with endoscopically active colitis (later labelled as Crohn's Disease) during a routine-screening colonoscopy despite being asymptomatic. She was subsequently started on sulfasalazine and budesonide. After 10 days, she presented to a hospital with fever and emesis. She was initially mildly hypotensive and tachycardic, but responsive to fluid resuscitation, with a new 2 L/min oxygen requirement. Physical examination was non-revealing.

Initial labs showed elevated C reactive protein and erythrocyte sedimentation rate, but normal white blood cell count (including absolute eosinophil count), lactic acid and liver function tests (LFTs). A respiratory viral panel was negative and chest, abdomen/pelvis CT revealed no significant abnormalities. Despite a lack of convincing laboratory data, sepsis secondary to pneumonia was suspected and the patient was started on empirical antibiotic therapy (using ceftriaxone and azithromycin). Her home sulfasalazine and budesonide were discontinued.

The next day, she developed a diffuse morbilliform rash and pancytopenia. Cytomegalovirus and Epstein-Barr virus IgM serologies as well as blood cultures were all negative. Urine cultures grew methicillin sensitive *Staphylococcus aureus*; however, she never had any urinary symptoms.

She later became hypotensive (again responsive to fluid resuscitation) and her LFTs rose. An abdominal ultrasound revealed mild gallbladder wall thickening without gallstones. Her antibiotics were broadened to levofloxacin, doxycycline and vancomycin due to concern for worsening sepsis. The patient's vital signs and labs subsequently normalised over the next 2 days. Despite uncertainty of the diagnosis, she was discharged after 5 days on doxycycline to complete a 14-day course of antibiotics.

After 16 days, the patient was advised to restart sulfasalazine. Within less than 10 hours of restarting the medication, she experienced abrupt-onset fevers, chills and emesis. When she arrived at the emergency room (ER), she had a temperature of 39.5°C, heart rate of 130 beats per minute, blood pressure (BP) of 116/64 mm Hg and required 3 L/min of oxygen. Physical examination was notable for rigours, but initial laboratory work-up (including eosinophil counts) and chest x-ray (CXR) revealed no significant abnormalities. Concern for sepsis led to initiation of meropenem. However, shortly after her admission, she developed distributive shock with BP readings dropping into the 70s/40s mm Hg and an associated lactic acid level of 4.3 mEq/L. She was aggressively fluid resuscitated with 8 L of saline and transferred to the intensive care unit (ICU) for initiation of vasopressor therapy. She developed anasarca, hyperemic skin, pancytopenia and mildly elevated LFTs.

Her antibiotics were broadened from meropenem to also include vancomycin and clindamycin, but blood cultures drawn at various times throughout the hospitalisation grew no bacteria. Transthoracic echocardiography and a right upper quadrant ultrasound identified no significant abnormalities. At this point, non-infectious aetiologies were considered and an extensive autoimmune work-up was negative with the exception of non-specific elevations in rheumatoid factor (271=IU/mL) and ferritin (144=ng/mL), as well as hypocomplementemia (C3=56 mg/dL, C4=11 mg/dL). With a non-specific autoimmune work-up and no identifiable source of infection, SIHS was suspected. Further testing for human herpes virus 6 serologies, lymphocyte transformation testing, interferon-gamma enzyme-linked ImmunoSpot analysis, was considered at one point. However, given the fact that these tests are not standardised, have suboptimal sensitivity and specificity profiles, they were deferred as the medical team felt that the results of such tests would not alter her overall management plan. Her antibiotics were discontinued and she received no autoimmune therapy, being managed with conservative measures only.

OUTCOME AND FOLLOW-UP

The patient's vital signs and laboratory values normalised and she was discharged 4 days after her second admission. She continued to remain symptom free for more than 1 year after discontinuation of sulfasalazine.

DISCUSSION

This case reinforces the well-known challenges in early identification of SIHS as it can mimic sepsis. It is also unique as it shows that such a relapse of SIHS after re-exposure can be drastically more severe and rapid in onset, compared with the initial exposure.

Of note, hypocomplementia, as seen in this patient, has been seen in other types of non-immediate drug hypersensitivity reactions (eg, Stevens-Johnson syndrome).[9] Further investigation of the complement pathway's involvement in the pathophysiology of SIHS is merited. Some experts recommend to check for recent active antibodies for Epstein-Barr virus, Cytomegalovirus (CMV), human herpesvirus (HHV)-6, or HHV-7 in patients with suspected drug rash with eosinophilia and systemic symptoms (DRESS) in general, including those with SIHS, since reactivation of those viruses can further complicated the course of recovery.[10] The diagnosis of SIHS (or DRESS) is still made predominantly based on clinical presentation. Nonetheless, on a case-by-case selection, new generation interferon-γ Enzyme-Linked ImmunoSpot (ELISPOT) assays and possibly lymphocyte transformation tests may be considered when no improvement is being observed and multiple drug reactions are being suspected.[11 12]

Clinicians, therefore, must maintain a high index of suspicion for SIHS in patients who have recently started sulfasalazine and subsequently develop signs of systemic inflammation without an identifiable source of infection. This high index of suspicion is vital to ensure that patients with SIHS are recognised quickly with timely initiation of appropriate treatment to reduce SIHS's morbidity and mortality, and most importantly to prevent future re-exposure.

Learning points

- Sulfasalazine-induced hypersensitivity syndrome (SIHS) is a serious adverse drug reaction associated with significant morbidity and mortality.
- Re-exposure to sulfasalazine in a patient with a history of SIHS can result in more rapid onset and severe expression of the disease.
- Clinicians must keep a high index of suspicion for SIHS in patients who have recently started sulfasalazine and subsequently develop signs of systemic inflammation without an identifiable source of infection so that patients with SIHS are recognised quickly to ensure that (1) they are not re-exposed to sulfasalazine and (2) appropriate treatment is initiated in a timely manner.

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