Serum sickness reaction to obinutuzumab in a patient with chronic lymphocytic leukaemia

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SUMMARY

Serum sickness (SS) is a known phenomenon; however, it is commonly missed due to vague symptoms, and is usually confounded by other aetiologies that present similarly. Obinutuzumab is a novel anti-CD20 antibody agent that has been approved for chronic lymphocytic leukaemia (CLL) treatment. At the time of approval, it was not linked to SS; however, this phenomenon has been recognised with other anti-CD20 agents like rituximab. SS remains a rare entity, but it is important to be recognised accurately and quickly in the appropriate circumstances, so that effective treatment with corticosteroids can be initiated to alleviate inflammatory symptoms. Here we present a patient with CLL who developed maculopapular rash, fever and polyarthritis and elevated inflammatory markers consistent with serum sickness triggered by obinutuzumab and was effectively treated with corticosteroids.

BACKGROUND

Obinutuzumab is a type II anti-CD20 monoclonal antibody. In 2013, it was approved for treatment of chronic lymphocytic leukaemia (CLL) in patients with other comorbidities. Upon its approval, several adverse reactions were observed, but serum sickness was not reported as one of them. Serum sickness disease is a type III immune complex-mediated hypersensitivity reaction. It was rarely reported with other anti-CD20 therapy like rituximab but has never been fully explored with newer generations. Here we present a very rare case of serum sickness related to obinutuzumab in a patient with CLL.

CASE PRESENTATION

A 63-year-old male patient, with a known history of CLL/small lymphocytic lymphoma. He was treated a year ago with rituximab for autoimmune haemolytic anaemia presumed secondary to CLL, however, this was discontinued after three infusions due to recurrent presyncope and lightheadedness. His haemoglobin has normalised by the time of discontinuing of rituximab. Eight months later, the patient started to develop progressive B symptoms (night sweats and fatigue) and interval scans suggested progressive adenopathy above and below the diaphragm, thus, he was started on treatment with venetoclax and obinutuzumab. Almost a week after his second infusion of obinutuzumab, he presented to the emergency room with complaints of high-grade fever up to 102 F, diffuse erythematous skin rash, joint pains and significant weakness that prevented him from ambulating freely and from doing basic daily activities.

Complete blood count assay showed neutropenia (absolute neutrophil count was 800 /uL, normal 1600–6100/uL), serum creatinine 1.8 mg/dL (normal 0.8–1.4 mg/dL). He had elevated inflammatory markers with erythrocyte sediment rate (ESR) of 94 mm/hour (normal 0–15 mm/hour), C reactive protein (CRP) of 83 mg/L (normal <8 mg/L) and serum complements were normal. Urine analysis showed +2 protein. Tumour lysis panel was normal. Blood cultures, urine analysis and chest X-ray did not reveal any evidence of infection. There were no other medications started recently within the same time frame of obinutuzumab. Given the constellation of fever, skin rash and polyarthralgia along with elevated inflammatory markers, and in the absence of evidence of an infectious process; a serum sickness disease related to obinutuzumab was entertained. We reviewed the literature and found that SS has been rarely reported with other anti-CD20 like rituximab. The patient was treated with prednisone 60 mg/day (0.5 mg/kg/day) with close follow-up. In retrospect, we also suspect that his intolerance to rituximab could be attributed to a milder form of SS.

DIFFERENTIAL DIAGNOSIS

Main differential diagnosis in a patient will CLL presenting with fever and rash would be an infectious process, either bacterial or viral. This patient had a complete infectious workup including blood cultures, urine cultures, chest imaging, and it was all negative. Other differential can include an autoimmune process like adult-onset Still's disease; however, given the chronological association with obinutuzumab, it is more likely related to the drug than an autoimmune disease. An allergic reaction to different drugs can present with rash and fever, but thorough medical history did not reveal any other new medications that the patient was taking.

TREATMENT

Generally, treatment of serum sickness involves discontinuation of the offending agent. But in our case, the patient had severe arthralgia and high-grade fever, so in addition to discontinuing obinutuzumab, we treated him with glucocorticoid. The recommended dose is oral prednisone 0.5–1 mg/kg/day followed by slow taper over weeks.

OUTCOME AND FOLLOW-UP

The patient was seen in clinic 1 week post-discharge, he had expressed significant improvement in joint

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pain and weakness as well as full resolution of rash and fevers while being maintained on prednisone 60 mg daily for a couple of weeks followed by slow taper. He remained only on venetoclax going forward with good control of his CLL.

DISCUSSION

CLL is the most common leukaemia in adults in the Western countries, accounting for one-third of all leukaemias in the United States.[1] Obinutuzumab is novel glycoengineered type II anti-CD20 monoclonal antibody that has been approved by United States Food and Drug Administration (FDA) in 2013 for treatment of CLL in combination with chlorambucil.[2] Subsequently another combined treatment with obinutuzumab and venetoclax has been tried and approved.[3]

Serum sickness (SS) is a type III hypersensitivity reaction which is immune-complex mediated.[4] These immune complexes can deposit or form on tissue, especially in joints, triggering an inflammatory response.[4] Clinically diagnosed with cardinal features of rash, fever and polyarthralgia, which begins 1 or 2 weeks after initial exposure to a causative agent.[4] Symptoms vary among patients and can be severe enough to cause high-grade fever or crippling polyarthralgia. The disease is self-limiting, and treatment with steroids can be given in severe cases. This phenomenon was first described in 1905 by Pirquet and Schick after administering horses' serum as antitoxin to treat diphtheria.[5] Elevated ESR and CRP are commonly seen in SS, as well as complement consumption, however these laboratory findings are not very sensitive.[6] Proteinuria is also commonly seen in SS.[7]

SS has not been linked to obinutuzumab on its approval and has since been only reported in one case by Saba and Logan, thus making it a rare complication of this treatment.[6] Their patient had received obinutuzumab as salvage therapy for CLL and had developed SS in two separate occasions. The patient's symptoms had improved dramatically with initiation of steroids, like our patient.

Rituximab is another anti-CD20 monoclonal antibody that is used for various haematological and rheumatological disorders. Rituximab typically can cause serum sickness within 1 week to 1 month of exposure; however, our patient's last dose of this drug was a year prior to his symptoms. Rituximab induced serum sickness (RISS) is also a rare occurrence, with a recent literature review only revealed 33 cases.[8] The review shows most of these cases are associated with rheumatological conditions (51%). The classic constellation of symptoms (fever, rash, arthralgia) only reported in 48.5% of the cases. The review also revealed longer duration for symptoms resolution with subsequent exposure compared with initial one. It also revealed shorter time to resolution in haematological conditions compared with rheumatological ones (1 vs 2.5 days).[8]

Treatment of SS depends on severity of symptoms. For mild cases, withholding the offending agent usually is enough. Analgesics and nonsteroidal anti-inflammatory can also be used for symptomatic relief. For more severe symptoms, treatment with corticosteroids can be beneficial, mainly with prednisone 1 mg/kg followed by a slow taper to avoid symptoms recurrence. In extreme and refractory cases, plasmapheresis can be attempted.[9]

With increased popularity of obinutuzumab in treatment of CLL, we predict more cases of SS will arise, and physicians should have high clinical suspicion for this adverse event, especially since treatment with corticosteroids is readily available and effective in alleviating the inflammatory symptoms.

Learning points

- Serum sickness (SS) is a known phenomenon that is associated with many drug exposures; however, it is commonly misdiagnosed due to vague symptoms and absence of highly sensitive diagnostic tools.
- SS symptoms can be very crippling that patients may require hospitalisation, mainly due to severe arthralgia and fever, especially in a vulnerable population (haematological malignancies).
- Accurate and quick recognition of this condition is very important, especially when treatment is readily available and helps improve symptoms dramatically.
- Serum sickness should be recognised as a potential complication of obinutuzumab and other anti-CD20 antibodies. Practitioners should have high clinical suspicion of such complications.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

REFERENCES

1 Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2021. *CA Cancer J Clin* 2021;71:7–33.
2 Reda G, Orofino N, Cassin R, *et al*. Treating chronic lymphocytic leukemia with obinutuzumab: safety and efficacy considerations. *Expert Opin Drug Saf* 2016;15:865–73.
3 Fischer K, Al-Sawaf O, Bahlo J, *et al*. Venetoclax and Obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 2019;380:2225–36.
4 Lawley TJ, Bielory L, Gascon P, *et al*. A prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med* 1984;311:1407–13.
5 Jackson R. Serum sickness. *J Cutan Med Surg* 2000;4:223–5.
6 Saba J, Logan AC. Obinutuzumab-induced serum sickness following salvage therapy for chronic lymphocytic leukemia. *Clin Case Rep* 2017;5:891–3.
7 Zhang Z, Xiang Y, Wang B, *et al*. Intestinal mucosal permeability of children with cefaclor-associated serum sickness-like reactions. *Eur J Pediatr* 2013;172:537–43.
8 Karmacharya P, Poudel DR, Pathak R, *et al*. Rituximab-Induced serum sickness: a systematic review. *Semin Arthritis Rheum* 2015;45:334–40.
9 Manko A, Besecker B. Plasmapheresis reverses ARDS in rituximab induced serum sickness. *Chest* 2014;146:269A.