Unexpected outcome (positive or negative) including adverse drug reactions

Nitrofurantoin-induced microangiopathic haemolytic anaemia and thrombocytopaenia in a patient with systemic lupus erythematosus

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Patients with systemic lupus erythematosus (SLE) may develop thrombotic thrombocytopaenic purpura (TTP) or TTP-like illness manifested by microangiopathic haemolytic anaemia (MAHA) and thrombocytopaenia. The distinction between active SLE and TTP is difficult because these entities share similar clinical features. Drug-induced TTP caused by an immune-mediated reaction have been documented for several drugs. Herein, we report a middle-aged Hispanic woman with long-standing SLE, who developed a TTP-like illness characterised by MAHA and thrombocytopaenia after exposure to nitrofurantoin. The patient responded well to plasmapheresis and immunosuppressive therapy and has remained clinically stable after 18 months of follow-up. To our knowledge, this is the first case that reports the association between nitrofurantoin and a TTP-like presentation.

BACKGROUND

The occurrence of thrombotic thrombocytopaenic purpura (TTP) in patients with systemic lupus erythematosus (SLE) has been previously reported.^{1–5} Also, SLE patients may present a TTP-like illness manifested by microangiopathic haemolytic anaemia (MAHA) and thrombocytopaenia.⁶ The distinction between these entities may be difficult because they share similar clinical features. Several drugs may induce immune-mediated TTP and MAHA.⁷ Nitrofurantoin, an antibiotic that is commonly used for the treatment of urinary tract infections (UTI), is known to cause blood dyscrasias, and immune-mediated reactions such as pulmonary fibrosis, autoimmune hepatitis and lupus-like syndrome.^{8–12} Herein, we present a middle-aged woman with long-standing SLE who developed thrombocytopaenia and MAHA after exposure to nitrofurantoin.

CASE PRESENTATION

A 56-year-old Puerto Rican woman was diagnosed with SLE in 1997 when she presented with tiredness, fever, non-scarring alopecia, malar rash, arthritis, leucopaenia and positive antinuclear antibodies (ANAs). She was treated with prednisone 15 mg daily and hydroxychloroquine 400 mg daily. For 13 years she remained in clinical remission and did not develop major organ involvement or other cytopenias.

In July 2010, she had an uncomplicated UTI treated with nitrofurantoin 100 mg twice daily for 7 days. One day after completing antibiotic therapy, she presented with multiple bruises in upper and lower limbs. She had no fever, headaches, hair loss, facial rash, photosensitivity, oral ulcers, arthralgias, myalgias, chest pain, dyspnoea, changes in mental status, seizures, haematuria or changes in urine output. While she was taking nitrofurantoin she did not have urticarial rash, pruritus, nausea, vomiting or shortness

of breath. Besides the presence of echymoses and petechiae, the physical examination was unremarkable.

INVESTIGATIONS

The initial laboratory evaluation revealed a white blood cell count of 5400/mm³, haemoglobin of 11.1 g/dl, platelet count of 6000/mm³, lymphocyte count of 1000/mm³, prothrombin time (PT) of 11.5 s, partial thromboplastin time (PTT) of 25.4 s, serum creatinine of 0.7 mg/dl and albumin of 3.9 g/dl. Urinalysis showed 0–2 RBC/hpf, 0–2 WBC/hpf and no nitrites, casts or proteinuria. Urine and blood cultures were negative. Fibrinogen level was 223 mg/dl (170–420 mg/dl) and D-dimer was 2.3 mg/l (0.4 mg/l–1.4 mg/l). The erythrocyte sedimentation rate was 31 mm/h. She was treated with platelet transfusions and dexamethasone (40 mg intravenously daily for 3 consecutive days) but she continued with severe thrombocytopaenia. The hospital course was complicated with severe anemia (8.8 g/dl), decreased haptoglobin (5.83 mg/dl (13–163 mg/dl)), increased lactate dehydrogenase (LDH) (1199 U/l (135–214 U/l)) and elevated total bilirubin (2.5 mg/dl) with predominance of indirect bilirubin. Coomb's test was negative. The peripheral smear revealed more than 5 schistocytes/hpf. ANA test was positive and anti-RNP antibodies were positive. Anti-dsDNA, anti-Smith, anti-SSA, anti-SSB and anti-cardiolipin antibodies were negative. The lupus anticoagulant was negative. C3 and C4 complement levels were normal. Glucose-6-phosphate dehydrogenase (G6PD) test was within normal range. Metalloprotease with thrombospondin type 1 motif 13 (ADAMTS-13) activity was within normal range.

TREATMENT

Upon recognition of MAHA, pulse glucocorticoid therapy (intravenous methylprednisolone 1 g daily for 3 days) and

daily plasmapheresis with fresh frozen plasma were started. Cyclophosphamide 750 mg intravenously was given on the 4th day after initiation of plasma exchange. She received a total of 11 courses of daily plasmapheresis and required two units of blood transfusions. By the 5th day of plasma exchange therapy, platelet count and haemoglobin level increased above 100 000/mm³ and 10 g/dl, respectively. After pulse glucocorticoid therapy, prednisone 60 mg/day was started. By day 11th of therapy, LDH level was within normal limits and platelets remained above 150 000 for 2 consecutive days. She did not develop renal or central nervous system (CNS) involvement.

OUTCOME AND FOLLOW-UP

Two weeks after discharge, during a follow-up visit, she was in stable condition, with an unremarkable physical examination and without findings of disease activity either of SLE or MAHA. Haematological parameters were normal with a white blood cell count of 4700/mm³, haemoglobin of 12.4 g/dl, platelets count of 187 000/mm³, lymphocyte count of 1600/mm³. After 20 months of follow-up, the patient remained clinically stable with normal haematological parameters. Her SLE also remained clinically quiescent. Prednisone was rapidly tapered down to 5 mg daily; she was kept on hydroxychloroquine 400 mg daily.

DISCUSSION

This patient, with long-standing SLE, presented with severe thrombocytopenia followed by MAHA after being treated with nitrofurantoin for an uncomplicated UTI. Prompt therapy with pulse glucocorticoid followed by high-dose prednisone combined with daily plasma exchange was initiated once MAHA was identified. At that moment she did not present any clinical manifestations suggestive of active lupus; neither elevated anti-dsDNA antibodies, increased erythrocyte sedimentation rate, nor decreased complement levels. However, she had persistent leucopenia prior to the development of thrombocytopenia and MAHA, a factor that may predict the development of an exacerbation in SLE patients.¹³

In SLE patients, the main haematological manifestations consist of anaemia, leukopenia, lymphopenia and thrombocytopenia.¹⁴ Anaemia of chronic disease is commonly seen in SLE patients, but autoimmune haemolytic anaemia and MAHA are less frequent.⁶ In view of the presence of haemolytic anaemia in the setting of fragmented red cells in peripheral blood our patient was diagnosed with MAHA. This type of haemolytic process may occur in SLE patients as well in other disorders such as TTP, haemolytic uraemic syndrome, HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, disseminated intravascular coagulopathy, vasculitis and antiphospholipid syndrome.⁶ In general, the prevalence of isolated MAHA in SLE is unknown, but in one study a frequency of 13% was reported.⁶

The coexistence of MAHA and severe thrombocytopenia may be the initial presentation of TTP.⁶ TTP is a microangiopathic thrombotic disorder characterised by MAHA, severe thrombocytopenia (<50 000), renal impairment, CNS abnormalities and fever. The coexistence of TTP and SLE is uncommon. In a Korean study of 1203 patients with SLE, 26 were found to have TTP at a

rate of 2.2%.⁴ TTP usually occurs in patients with SLE³ with moderate-to-severe disease activity.⁴ The clinical overlap between both entities makes difficult to distinguish whether the clinical features are secondary to TTP or SLE exacerbation. Except for cytopenias, the fact that our patient did not present any other clinical or serological features indicative of SLE activity, favours MAHA or early TTP instead of SLE exacerbation. On the other hand, classic TTP is characterised by the complete pentad of clinical features, but our patient exhibited only two clinical manifestations. The latter may be possible because she was initiated on pulse glucocorticoid and plasma exchange at the recognition of MAHA; thus, the chosen therapeutic regimen appeared to halt the progression to TTP.

Bacterial infections have been linked to the development of TTP; these are usually severe or complicated infections.¹⁵ Furthermore, a recent study suggested an association of UTIs with TTP, but it remains uncertain if these infections, or their severity, actually caused the TTP.¹⁶ Because our patient had an uncomplicated UTI that rapidly resolved with nitrofurantoin treatment we believed that it is very unlikely that the TTP-like illness was triggered by the UTI.

SLE patients may have a similar proportion of adverse drug reactions as the general population,¹⁷ but some studies establish that they may be at increased risk for hypersensitivity reactions and disease flares to certain antibiotics, in particular to sulphonamides.¹⁸ Nitrofurantoin, an antibiotic that is commonly used for the treatment of UTIs, is an agent known to cause haemolytic reactions in the setting of G6PD deficiency.¹⁹ To our knowledge, the association between nitrofurantoin and MAHA and/or TTP has not been reported. However, this medication has been associated with several immune-mediated reactions such as pulmonary fibrosis, autoimmune hepatitis, lupus-like syndrome and the development of antinuclear antibodies in normal subjects exposed to this antibiotic.^{8–12} In our patient, the development of thrombocytopenia and MAHA occurred shortly after the completion of nitrofurantoin treatment. Since she did not have other precipitating factors, including her SLE, we propose that nitrofurantoin caused the TTP-like presentation in our patient.

The current literature suggests that idiopathic or autoimmune-related TTP is associated with a deficiency of ADAMTS-13 activity.^{20–21} However, this association is controversial based on few studies that show no association between ADAMTS-13 activity and connective tissue diseases, in particular SLE.^{22–23} On the other hand, drug-induced TTP is typically not associated with a low activity of ADAMTS-13.⁷ Drug-induced TTP caused by an immune-mediated reaction has been previously documented with quinine, ticlopidine and clopidogrel.⁷ The clinical scenario in drug-induced TTP is characterised by a sudden onset of symptoms after drug exposure followed by a rapid recovery after institution of plasmapheresis. In most cases of drug-induced TTP, the cause-effect relation of the offending drug is not explicit, but in our case there was a strong connection of drug exposure to the onset of MAHA and thrombocytopenia.

In summary, we report a Hispanic woman with SLE presenting with a TTP-like illness manifested by MAHA and thrombocytopenia after treatment with

nitrofurantoin. Distinguishing drug-induced MAHA and thrombocytopaenia from SLE exacerbation could be challenging because both entities share similar clinical features. Patients with SLE exhibiting a TTP-like illness are treated with plasmapheresis with immunosuppressive agents to avoid a nearly 100% death rate of untreated TTP. Fortunately, our patient had an excellent and rapid response to this therapy. To our knowledge, this is the first case reporting the association between nitrofurantoin and TTP-like illness. Clinicians should be aware of this unusual presentation, and keep in mind the immune-related adverse effects induced by nitrofurantoin.

Learning points

- ▶ Nitrofurantoin may cause a thrombotic thrombocytopaenic purpura (TTP)-like illness manifested by microangiopathic haemolytic anaemia and thrombocytopaenia.
- ▶ Distinguishing TTP-like illness from SLE exacerbation could be challenging because both entities share similar clinical features.
- ▶ Clinicians should keep in mind the immune-related adverse effects induced by nitrofurantoin.

Competing interests None.

Patient consent Obtained.

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