New disease

DRESS syndrome and thrombotic thrombocytopenic purpura: are they related?

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Summary

A middle-aged man diagnosed with a drug reaction with eosinophilia and systemic symptom (DRESS) syndrome, secondary to phenytoin use, subsequently developed thrombotic thrombocytopenic purpura. The patient improved with steroids and plasmapheresis. Their diagnosis can be challenging, and an early recognition and treatment are critical owing to their high mortality rates. Both diseases are thought to be of an autoimmune origin, and a potential relationship between them led to the consideration of the DRESS syndrome as an aetiology for thrombotic thrombocytopenic purpura in this case. We concluded that two possibilities exist: some type of antibody developed during the clinical presentation of DRESS syndrome and subsequently resulted in an inhibition of a disintegrin and metalloproteinase with a thrombospondin type-1 motif, member 13 (ADAMTS13) leading to thrombotic thrombocytopenic purpura, or perhaps this patient's autoimmune predisposition to thrombotic thrombocytopenic purpura contributed to the drug reaction.

BACKGROUND

Thrombotic thrombocytopenic purpura is a rare, life-threatening, multisystem disorder characterised by the pentad of fever, neurological impairment, microangiopathic haemolytic anaemia, renal impairment and thrombocytopenia. An early recognition and a prompt treatment are required to prevent mortality. It may be idiopathic or secondary to various factors such as cancer, medications, pregnancy or HIV. Autoimmune conditions including systemic lupus erythematosus, Hashimoto's thyroiditis, psoriasis and immune thrombocytopenic purpura have also been associated with the disease.¹ Patients with an existing autoimmune condition are thought to be genetically susceptible to acquire other types of autoimmune disorders. One such condition is the drug reaction with eosinophilia and systemic symptom (DRESS) syndrome, which has an estimated incidence ranging from 1 in 1000 to 1 in 10 000 drug exposures. DRESS is a life-threatening syndrome that includes a severe skin eruption, fever, haematological abnormalities and internal organ involvement.²

We report the first case of a patient with DRESS syndrome secondary to an anticonvulsant medication, who subsequently developed thrombotic thrombocytopenic purpura within 3 months.

CASE PRESENTATION

A 50-year-old man with a new onset of seizures post-ischaemic stroke was treated with phenytoin. A month later, he presented to the emergency department with hives and a fever greater than 100°F for 4 days and a maculopapular rash on his trunk and limbs with some pustules. He denied having any other symptoms. His medical history was also significant for hypertension. He denied an abuse of tobacco, alcohol and/or drugs.

None of his family members suffered from autoimmune diseases.

Laboratory findings were significant for elevated white blood cell count (14.5 K/ μ l) with elevated neutrophils (8.97 K/ μ l), eosinophilia (1.6 K/ μ l), anaemia (haemoglobin 10.8 g/dl) and thrombocytopenia (133 K/ μ l). He also had elevated aspartate transaminase (427 IU/l), alanine aminotransferase (625 IU/l) with a high alkaline phosphatase (163 IU/l) and normal bilirubin levels. Infectious work up (urine and blood cultures), hepatitis panel (hepatitis C antibody and RNA quantity, hepatitis B antibody and antigen, hepatitis A antibody) and autoimmune liver screen (mitochondrial antibody, smooth muscle antibody, liver-kidney microsomal antibody screens) were all negative. He was found to have marginally positive antinuclear antibody, a past infection with Epstein-Barr virus, a negative HIV 1 and 2 antibody and a negative human herpes virus-6 immunoglobulin M. A skin biopsy was suggestive of vasculitis.

The patient's symptoms fit the criteria for the diagnosis of DRESS syndrome. He was subsequently treated with a high-dose solumedrol and then discharged home with prednisone. His symptoms resolved slowly and steadily.

Three months later, he was seen again in the emergency department for complaints of aphasia and altered mental status for 1 day. He was haemodynamically stable. A CT of the head was negative for any new acute intracranial haemorrhagic or ischaemic stroke, and his neurological examination had returned to normal in the emergency department. However, his laboratory findings were significant for renal impairment (BUN 20, creatinine 1.67 mg/dl), anaemia (haemoglobin 8.5 g/dl), white blood cell count (9.7 K/ μ l) and thrombocytopenia (platelet count 14 K/ μ l), reticulocyte count 2.6% (absolute of 74.1 K/ μ l and index 0.69) along with elevated lactate dehydrogenase (689 IU/l) and a low haptoglobin (<8.00). His liver profile was within

normal limits. A coagulation profile was unchanged: prothrombin time 13.6 s, international normalised ratio 1.06, partial thromboplastin time 33 s. A disseminated intravascular coagulation profile was negative (fibrinogen level 426 mg/dl, D-dimer >3000 ng/ml). A peripheral smear showed schistocytes. The diagnosis of thrombotic thrombocytopenic purpura was made; the patient was thus immediately started on plasmapheresis. Further laboratory studies to investigate the type of disease revealed a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency with inhibitors in his plasma.

INVESTIGATIONS

The investigations used to classify the type of thrombotic thrombocytopenic purpura included assessment of ADAMTS13 activity and inhibitors. He was found to have a severe deficiency of ADAMTS13 activity with a level of <5% (normal >67%) and 1.6 IU inhibitors (inhibitor units reference range: ≤0.4 IU).

ADAMTS13 activity is measured by fluorescence resonance energy transfer with a synthetic substrate (VWF73 substrate). ADAMTS13 inhibitor is determined using mixing studies; one inhibitor unit is defined as the concentration of inhibitor with an ability to reduce the ADAMTS13 activity of an equal volume of normal pooled plasma by half. The ADAMTS13 antibody assay detects immunoglobulin G antibody serologically by an ELISA.³

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for his initial presentation of fever and rash was broad. An infectious process, such as HIV, Epstein-Barr virus, *Staphylococcus bacteraemia* etc, was initially thought to be the cause. This was quickly ruled out based on results of the initial work up (negative antibodies and cultures). It is important to rule out underlying infectious aetiology early, as steroids should not be used without antibiotics in such cases. Autoimmune disorders were also ruled out with negative autoimmune work up. However, manifestation of the patient's symptoms shortly after the initiation of a new drug prompted a further investigation of drug reaction syndromes, such as Stevens Johnson syndrome and toxic epidermal necrolysis. The manner in which the rash presented helped rule out these syndromes: both the aforementioned diseases have typical painful lesions of the skin and mucous membranes that develop into blisters with extensive detachment of the epidermis. This was not consistent with our patient's rash. Our patient had multiple organ involvement and eosinophilia, that is, only prominent in certain cases of drug reactions, such as the DRESS syndrome. The diagnosis of DRESS was eventually established using the RegiSCAR scoring system. Our patient fulfilled six of the seven criteria, strongly supporting this as a case of DRESS syndrome.^{4 5}

During his second admission, when he presented with neurological symptoms and altered mental status, the most important step to guide treatment was to rule out any new stroke, which was done using a CT of the head. The findings of haemolytic anaemia and thrombocytopenia steered the differential diagnosis towards haematological disorders such as idiopathic thrombocytopenic purpura, haemolytic uraemic syndrome and thrombotic

thrombocytopenic purpura. Idiopathic thrombocytopenic purpura is a diagnosis of exclusion. It is especially important to quickly arrive at a diagnosis since both haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura require an urgent plasmapheresis to decrease mortality. Our patient's insidious presentation of thrombocytopenia, haemolytic anaemia, and renal failure was more consistent with both the aforementioned diseases. The additions of fever and change in mental status were more consistent with thrombotic thrombocytopenic purpura.⁶

TREATMENT

Upon the diagnosis of thrombotic thrombocytopenic purpura, the patient was immediately started on daily plasmapheresis. He received a total of 15 sessions of plasmapheresis during his stay without complications. He was discharged 20 days later after his platelet count had increased to an appropriate level (>15 K/μl). Upon discharge, most of his laboratory findings had returned to normal, except for his renal function that took 2 months to recover (creatinine improved to his baseline of 1.1 mg/dl).

OUTCOME AND FOLLOW-UP

He continues to be seen as an outpatient for treatment with a plasmapheresis taper (one session every other day then twice weekly) to be adjusted until his platelet counts return to the baseline.

DISCUSSION

Drug reaction with eosinophilia and systemic symptoms is a rare, life-threatening, drug-induced illness characterised by widespread polymorphic eruption, fever and multivisceral involvement, most commonly hepatitis and myocarditis. The drugs most commonly associated with this syndrome are allopurinol, carbamazepine, phenobarbital and sulphasalazine.^{7 8} The syndrome has a delayed onset of 2–6 weeks after the initiation of a drug therapy and can persist despite discontinuation of the culprit drug. The pathogenesis of the DRESS syndrome is only partially understood. Different mechanisms have been implicated in its development. One such hypothesis includes the presence of detoxification defects leading to reactive metabolite formation and subsequent immunological reactions. Others attribute it to slow acetylation and genetic predisposition.^{9 10}

The pathogenesis of thrombotic thrombocytopenic purpura has been extensively studied. When exposed to high shear stress in the microcirculation, von Willebrand factor and platelets are prone to form aggregates. This propensity of von Willebrand factor and platelets to form microvascular thrombosis is mitigated by ADAMTS13 that cleaves to an unusually high-molecular-weight von Willebrand factor. Deficiency of ADAMTS13, due to autoimmune inhibitors in patients with acquired thrombotic thrombocytopenic purpura, leads to von Willebrand factor-platelet aggregation and microvascular thrombosis.¹¹

Our patient has an acquired form of the disease possibly induced by the DRESS syndrome.

A trend to develop autoimmunity has been noted in 30% of patients with acquired thrombotic thrombocytopenic purpura. The remarkable efficiency of the anti-CD20 monoclonal antibody rituximab in refractory or chronic

relapsing forms provides an additional indirect argument to consider acquired thrombotic thrombocytopenic purpura as an autoimmune disease.¹² Both the rare diseases discussed here have a component of an autoimmune process.

Upon review of this case, we concluded that two possibilities cannot be excluded: some type of antibody developed during the clinical presentation of DRESS syndrome and subsequently resulted in inhibition of ADAMTS13 leading to thrombotic thrombocytopenic purpura; or perhaps this patient's autoimmune predisposition to thrombotic thrombocytopenic purpura contributed to the drug reaction.

The DRESS syndrome is predominantly treated with steroids for a prolonged time, while thrombotic thrombocytopenic purpura treatment includes plasmapheresis and/or steroids in addition to immunomodulators such as rituximab.¹² All these agents target the immune and inflammatory system.

Learning points

- To consider drug reaction with eosinophilia and systemic symptom (DRESS) syndrome as a possible cause for thrombotic thrombocytopenic purpura.
- To consider the relationship between autoimmune disorders and thrombotic thrombocytopenic purpura.
- Patients with one type of autoimmune condition are genetically susceptible to acquire other forms of autoimmune disorders.

Competing interests None.

Patient consent Obtained.

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