

DRESS syndrome with thrombotic microangiopathy revealing a Noonan syndrome

Case report

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Abstract

Rationale: The life-threatening drug rash with eosinophilia and systemic symptoms (DRESS) syndrome occurs most commonly after exposure to drugs, clinical features mimic those found with other serious systemic disorders. It is rarely associated with thrombotic microangiopathy.

Patient concerns: We describe the unique case of a 44-year-old man who simultaneously experienced DRESS syndrome with thrombotic microangiopathy (TMA) after a 5 days treatment with fluindione.

Diagnoses: Clinical evaluation leads to the discovery of an underlying lymphangiomatosis, due to a Noonan syndrome.

Interventions: The anticoagulant was withdrawn, and corticosteroids (1 mg/kg/day) and acenocoumarol were started.

Outcomes: Clinical improvement ensued. At follow-up the patient is well.

Lessons: The association of DRESS with TMA is a rare condition; we believe that the presence of the underlying Noonan syndrome could have been the trigger. Moreover, we speculate about the potential interrelations between these entities.

Abbreviations: DRESS = drug reaction with eosinophilia and systemic symptoms, LVEF = left ventricular ejection fraction, NS = Noonan syndrome, TMA = thrombotic microangiopathy, TTP = thrombotic thrombocytopenic purpura, VEGF-C = vascular endothelial growth factor-C.

Keywords: fluindione, lymphangiomatosis, thrombotic thrombocytopenic purpura

1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and life-threatening idiosyncratic drug reaction occurring 2 to 8 weeks after exposure to an offending agent.^[1] Among the most commonly implicated medications are allopurinol, sulfonamides, and aromatic anticonvulsants such as phenytoin, phenobarbital, and carbamazepine. The association between thrombotic microangiopathy is exceedingly rare.^[2,3]

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MB and MC equally contributed to this work.

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2. Case report

A 44-year-old man, with a history of asthma and Charcot-Marie-Tooth disease, was initially admitted to another hospital for the sudden onset of fever, erythematous rash and 5 days after receiving the oral anticoagulant fluindione after ankle sprain repair. The patient was 1.84 m tall and presented mild dysmorphic features (thick lips with prominent nasolabial folds, epicanthal folds, low-set posteriorly rotated ears, short neck, high anterior and low posterior hairline, pectus carinatum, and arachnodactyly; Fig. 1A–C) besides skin rash, physical examination revealed diffuse lymphadenopathy, hyperlaxity of the hands and wrists, and foot deformities (high arch, or *pes cavus*, and hammer toes) typical of Charcot-Marie-Tooth disease (Fig. 1D). The patient reported that his grandfather had similar dysmorphic features.

Laboratory tests showed hemolytic anemia with schistocytes on a peripheral smear, thrombocytopenia, eosinophilia ($11 \times 10^9/L$), elevated lactate dehydrogenase level and renal failure with proteinuria and hematuria. His condition rapidly worsened with jaundice, oliguria, and hemodynamic instability. A renal biopsy showed microangiopathy characterized by wrinkling of glomerular capillaries, parietal arteriolar edema, focal glomerular ischemia, widening of the subendothelial space, and focal glomerular ischemia (Fig. 2A). Trans-thoracic echocardiography demonstrated left ventricular thrombus, endocardial infiltration of both ventricles compatible with an eosinophilic cardiomyopathy and moderate left ventricular dysfunction (left ventricular ejection fraction, LVEF: 45%) without chamber dilatation (Fig. 2B). The patient was transferred to our hospital for



Figure 1. Dysmorphic features. (A) Thick lips with prominent nasolabial folds, high anterior airway, short neck. (B) Low-set posteriorly rotated ears, low posterior hairline. (C) Pectus carinatum. (D) Foot deformities typical of Charcot-Marie-Tooth disease.

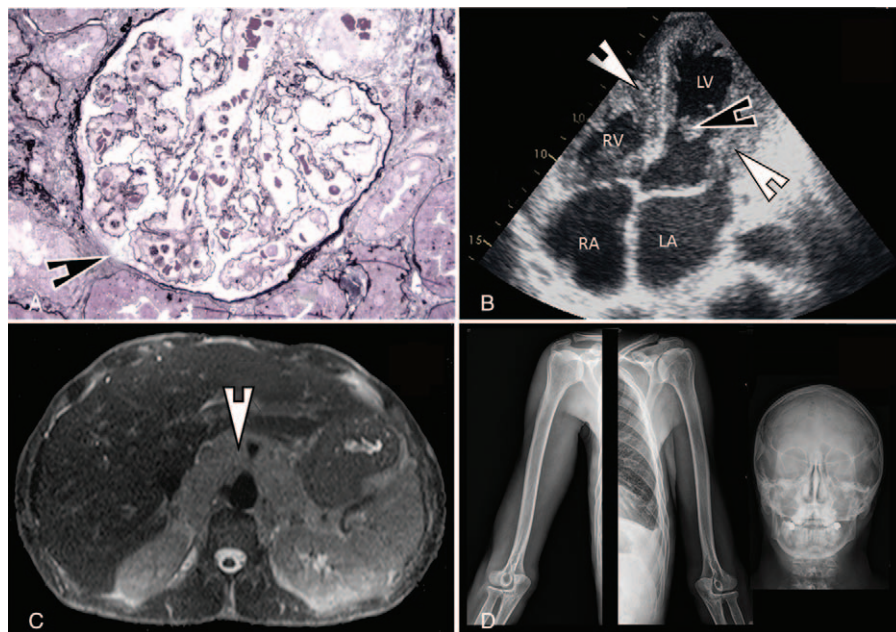


Figure 2. (A) Glomerulus showing wrinkling of capillary walls, parietal arteriolar edema, focal glomerular ischemia, and widening of the subendothelial space (arrows) (Jones' basement membrane stain, $\times 400$). (B) Trans-thoracic echocardiography showing a nondilated left ventricle with infiltration of both left and right ventricles endocardium (thick arrows) and a left ventricular thrombus (thin arrow). (C) MRI (T2 weighted images) showing a diffuse infiltration of the retroperitoneal space surrounding the aorta and the caval vein with no mass effect. (D) Representative x-ray images (from left to right: right and left humerus and shoulder girdle, skull) showing normal bone structure without pathologic features. LA=left atrium, LV=left ventricle, RA=right atrium, RV=right ventricle.

investigations. Echocardiography-guided endomyocardial biopsy was performed upon arrival; histology showed focal thrombotic microangiopathy and scattered foci of myocardial necrosis.

Clinical (fever, exanthema, and lymphadenopathy) and laboratory (eosinophilia) findings raised the suspicion of a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome associated with thrombotic microangiopathy (TMA), as suggested by thrombocytopenia, anemia, and ischemic injury of kidney and heart, as well as kidney histology. The offending agent was suspected to be the vitamin K-antagonist anticoagulant fluindione. The anticoagulant was immediately withdrawn, and corticosteroids (1 mg/kg/day) and acenocoumarol were started with rapid clinical improvement.

Search for the FIP1L1–PDGFRA rearrangement was negative, thus excluding a primary hypereosinophilic syndrome. Mild deficiency of ADAMTS13 (43% of plasma levels) and high anti-ADAMTS13 titers were found (40 UI; normal <15 UI) suggesting thrombotic thrombocytopenic purpura (TTP). Diffuse lymphadenopathy prompted us to perform whole body MRI. The exam showed mediastinal and retroperitoneal lymphangiomatosis (Fig. 2C). There was no bone involvement, as confirmed by plain radiographs of the humerus, forearm, shoulder girdle, femur, leg, foot, and skull that proved normal (Fig. 2D). The extensive lymphatic involvement as well as morphological features evoked an underlying genetic abnormality: Noonan syndrome (NS) was considered despite his height. Plasmatic vascular endothelial growth factor-C (VEGF-C) levels were normal (41 pg/mL; normal < 115 pg/mL). Genetic analysis showed a mutation in the *SOS2* gene but a normal karyotype, confirming the clinical suspicion of NS.

Four years after diagnosis the patient is well and laboratory findings are normal with no eosinophilia; echocardiography shows no signs of thrombosis with normal LVEF.

3. Discussion

Difficult to diagnose and a major mimicker, DRESS is characterized by the presence of at least 3 of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis.^[1] Multiple organ involvement can occur, as in our patient, including myocarditis, pericarditis, interstitial nephritis, necrotizing granulomatous vasculitis of the kidney, encephalitis, meningitis, colitis, thyroiditis, pancreatitis, and myositis.^[4] Fluindione is the most prescribed oral anticoagulant in France (it represents nearly 80% of all prescribed anticoagulants).^[5] Since 1987, hepatic and renal adverse effects through immunoallergic mechanisms have been well documented with fluindione.^[5] Association of DRESS syndrome to fluindione was first described by Sparsa et al.^[6] Since then, 36 cases of DRESS syndrome associated to fluindione were reported in a 10 years period.^[7] The mean time-to-onset of DRESS syndrome after fluindione treatment was 28.4 days; occurrence was more rapid in patients with previous hypersensitivity syndrome with a chemically related drug. Kidneys and liver were the most frequently involved organs, but no cases of cardiac involvement were observed. Moreover, the co-occurrence of TMA was never reported.

TMA represents a heterogeneous group of syndromes sharing the classic triad of thrombocytopenia, microangiopathic hemolytic anemia, and organ injury (due to microvascular occlusion and ischemia). Frequently triggered by infections, drug-induced TMA has also been described.^[8] Up to now, only 2 cases reporting a potential association between DRESS and thrombotic

thrombocytopenic purpura, a type of TMA, have been published.^[2,3] ADAMTS13 testing can be useful in differentiating TTP from others TMA, as in our case.^[9]

Lymphangiomatosis is a rare disease characterized by lymphatics proliferation in different organs. When occurring in bones (preferentially the humerus, shoulder girdle, pelvis, skull and mandible) it is called Gorham–Stout or “vanishing bone” disease; typical features are massive osteolysis followed by fibrotic replacement. When proliferation occurs in soft tissues (mainly the lung, spleen, mediastinum, and retroperitoneum), the disease is referred to as disseminated (also called generalized or diffuse) lymphangiomatosis.^[10] Often considered as 2 separate entities, recent data suggest that they could represent 2 forms of the same process sharing a common pathogenetic mechanism: altered lymphangiogenesis.^[11] Circulating levels of lymphangiogenic factors, including the VEGF, seem to be relevant markers of disease activity.^[12] Disseminated lymphangiomatosis can be associated with NS, a genetically heterogeneous autosomal dominant disorder characterized by facial dysmorphism, short stature, heart defects and lymphatic vascular disease;^[13] mutations in *SOS2* are associated with normal stature, as in our patient.^[14] Although association between abnormally low VEGF-C levels and NS has been reported,^[15] we detected normal VEGF-C levels in our patient.

We hypothesize that NS could have been the backbone of the development of both DRESS and TMA with fluindione as trigger. Immune dysregulation has been described in NS^[16] and could have been playing a facilitating role in the development of DRESS syndrome, whose pathogenesis is immune mediated. Coagulation defects, and among them platelet dysfunction, is a typical feature of NS; a conceivable role for such defect in TMA can therefore be claimed.^[17] A single case of TTP associated with NS has been previously described.^[18] Instead, although the patient was also suffering from Charcot–Marie–Tooth disease, we could not find a link between this disorder with the development of DRESS and TMA.

4. Conclusion

We report the unique presentation of a DRESS syndrome associated with TMA, most likely induced by fluindione, occurring in a patient with a serendipitously revealed NS. This case suggests an intricate interplay between both acquired and congenital defects in the immune and coagulation system contributing to the final clinical picture.

Ethical approval was not necessary since it is the retrospectively description of case of an anonymized patient; moreover, the patient in the study has been treated according to guidelines and no experimental procedures or medications have been used. Patient gave his informed consent.

Author contributions

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