Vasculitis and nephritis caused by pramipexole, a second generation dopamine agonist

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Pramipexole is a second-generation aminothiazole dopamine 2 (D2) receptor agonist that is approved for the treatment of Parkinson's disease, primary tremor, and the restless leg syndrome (1-3). Vasculitis and nephritis have not been so far associated with the use of pramipexole.

A 74-year-old man presented with a pruritic rash and oedema affecting the buttocks and both lower limbs. He had hypertension and permanent atrial fibrillation that were managed with doxazosin, amiodarone, and warfarin, and reported a history of heavy alcohol consumption in the past. Three weeks earlier pramipexole was prescribed with the dose increased up to 1.4 mg daily for the treatment of a primary tremor, and 2 weeks after pramipexole was started the patient noted petechiae and a pruritic rash involving the skin over the right buttock and both lower limbs. At this time, platelets were 10^5 x 10^9/L, fibrinogen 345 mg/dL, the international normalized ratio (INR) 2.7, and the activated partial trombophlastin time (aPPT) 28 seconds. Over the subsequent days the rash became worse and the patient was admitted to the hospital.

The patient denied recent alcohol misuse or the taking of over-the-counter or illicit drugs and did not recall gastrointestinal or respiratory symptoms, arthralgias, hematuria, melena or hematochezia or any other overt bleeding during the last month preceding admission. On physical examination, he was afebrile, occasional bibasilar crackles were noted in his lungs, and no cardiac murmur was heard; there was no abdominal tenderness with no palpable hepatosplenomegaly or lymphadenopathy. Petechiae and a palpable, non-tender purpura with pitting oedema affecting the buttocks and both lower limbs were observed; the skin over the trunk, face, and arms was spared.

Blood tests showed leucokytosis (12.3 x 10^9/L), with neutrophilia (11.1 x 10^9/L) and eosinophilia (8.50 x 10^9/L), and low platelet counts (25 x 10^9/L); enzymes, electrolytes, and renal and liver function tests were normal. C-reactive protein was 117 mg/L (0-6 mg/L), the erythrocyte sedimentation rate 32 mm/hour (1-20 mm/hour), and INR 2.8 with a normal aPTT. Testing of the urine was positivefor protein and blood and urine microscopy showed several erythrocyte and granular casts and > 100 dysmorphic erythrocytesper 10^6/L with no leukocytes; the urine protein:creatinine ratio was 0.15 (normalrange < 0.04) and a 24-hour proteinuria was 1.7 grams. These findings on urinalysis were confirmed in different successive determinations during the patient's hospital stay. A chest X-ray was normal and abdominal ultrasonography and computed tomography were also unremarkable.

We made a provisional diagnosis of Schönlein-Henoch purpura due to pramipexole, and stopped the medication; the serum immunoglobulin A concentration, however, was normal. Anti-platelet glycoprotein IIb/IIIa antibodies were detected on the surface of platelets but not in the serum from the patient. A skin biopsy was performed, which showed leukocytoclastic vasculitis involving the vessels in the papillary and mid-dermis, as well asspongiosis and moderate orthokeratosis; no IgA deposits were found in the dermal vesselwalls. Other potential causes of vasculitis were ruled out based on negative results for a wide spectrum of infectious and immune tests (Table I). The rash, peripheral eosinophilia, and microscopichematuria resolved completely and platelet counts returned to normal within one week of stopping pramipexole and the patient was discharged. The C-reactive protein concentration became normal and a search for anti-platelet glycoprotein IIb/IIIa was negative 3 weeks later, though proteinuria took 10 weeks to resolve. At the follow-up visits 2, 4, and 6 months after his discharge, the patient was asymptomatic with no evidence of purpura; platelet counts, urinalysis, and renal function tests remained normal and anti-platelet glycoprotein IIb/IIIa were not detected. We did not administer a re-challenge dose of pramipexole for ethical reasons, and he was advised of the potential risks associated with a hypersensitivity vasculitis due to pramipexole.

The clinical and histological featuresof this patient and his course are highly consistent with a hypersensitivity reaction to pramipexole. This is lent support by the temporal relationship, the 3-week delay between starting treatment with pramipexole and the onset of symptoms, and the rapid and almost complete recovery over a few weeks after the medication was stopped. Furthermore, assessment with the use of an objective causality tool indicated a relationship of probability between pramipexole therapy andthe occurrence of purpura and vasculitis (4). Other potential causes of vasculitis were also appropriately ruled out upon history, clinical findings, and laboratory studies.

The association of vasculitis and nephritis with a moderate to severe thrombocytopenia is an additional issue of interest in this case. Platelet destruction appeared to be mediated by IgG to surface glycoprotein IIb/IIIa, was transient as it resolved within days of stopping pramipexole, and treatment with corticosteroids or other immunosuppressive medications was not required. This reflects the typical course of a drug-induced thrombocytopenia (5).However, we could not rule out that other mechanisms, such as aggregation, sequestration or non-immune destruction of platelets in the kidney or the inflamed vascular walls, were also at least in part implicated.

Except for the increased risk of sleep attacks and vivid hallucinations (6), the safety profile of pramipexole is otherwise favorable. To the best of our knowledge, there is no report of vasculitis or nephritis or other immune-mediated adverse events due to pramipexole. Our case history demonstrates that a drug-induced systemic vasculitis may occur while on treatment with pramipexole. However, due to the non-specific presentation and the absence of typical serological markers the diagnosis could be challenging and a high index of suspicion is required.

Table I. Results of infectious and immune tests done to rule out other potential causes of vasculitis.

Antinuclear antibodies	Neg.
ANCA	Neg.
Antiphospholipid antibodies	Neg.
Lupus anticoagulant	Neg.
Rheumatoid factor	Neg.
Cryoglobulins	Neg.
Anti-mitochondrial antibodies	Neg.
C3 and C4 levels	Normal
HBsAg	Neg.
Anti-HBsAg antibodies	Neg.
Anti-HCVantibodies	Neg.
Anti-HIVantibodies	Neg.
Anti-influenza (IgG and IgM) Abs	Neg.
Anti-Coxsackie (IgG and IgM) Abs	Neg.
Anti-adenovirus (IgM) antibodies	Pos. 1:25
Anti-adenovirus (IgG) antibodies	Neg.
Anti-cytomegalovirus (IgG and IgM)	Neg.
Anti-Epstein-Barr virus (IgG and IgM)	Neg.
Anti-herpes simplex 1/2 (IgG and IgM)	Neg.
Anti-*M. pneumoniae* (IgG and IgM)	Neg.
Anti-Echo virus (IgG and IgM)	Neg.

ANCA: anti-neutrophil cytoplasmic antibodies; HbsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

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