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NSAIDS LINKED TO IGA-MEDIATED HYPERSENSITIVITY VASCULITIS AND PURPURA FULMINANS-LIKE ERUPTION

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ABSTRACT

Background: IgA vasculitis and hypersensitivity reactions following exposure to non-steroidal anti-inflammatory drugs (NSAIDs) are very rarely associated with purpura fulminans (PF). The latter is a coagulation event characterised by decreased levels of protein C and a rapidly progressive purpuric rash, often leading to ischaemia, amputations and death.

Case summary: A previously healthy 66-year-old man presented with a vasculitic rash and abdominal pain following exposure to naproxen (NSAID), which quickly deteriorated to purpura fulminans-like eruption and skin necrosis, mainly involving the face and hands. The presence of IgA sediments on skin biopsy and decreased levels of complement as well as protein C pointed to an immune-mediated inflammatory process. Dramatic clinical escalation with immediate risk to organs and life required an aggressive and broad-spectrum therapeutic approach in an intensive care setting. Clinical improvement and complete reconstitution of protein C were achieved following plasma exchange with fresh frozen plasma (FFP) and immunosuppression with glucocorticoids with no persistent organ damage.

Conclusions: This rare case illustrates the catastrophic cross links between NSAIDs, IgA-mediated hypersensitivity vasculitis and purpura fulminans-like syndrome. A high index of suspicion is required for the evaluation of environmental exposures such as drugs and infections in patients with vasculitis and/or purpura. A rapid and comprehensive therapeutic approach should be implemented to avoid multi-organ damage, amputations and death. Complete avoidance of the offending agent is key for future prevention of recurrence.

KEYWORDS

NSAIDs, vasculitis, purpura fulminans, IgA vasculitis, drug hypersensitivity

LEARNING POINTS

- This case illustrates a rare cross link between a commonly used drug (NSAIDs) and severe, life-threatening hypersensitivity reactions (IgA vasculitis and purpura fulminans-like eruption).
- These events require a high index of suspicion and emphasise the importance of considering environmental exposures such as drugs in the immediate diagnosis of both conditions.
- In addition to long-term drug avoidance, early and aggressive interventions are required to avoid organ damage, amputations or death.

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INTRODUCTION

Vasculitides are a diverse group of diseases, characterised by inflammation of blood vessel walls that can have localised or systemic involvement. While some hypersensitivity responses are mild and skin-dominant, in others the reaction can be fulminant and life-threatening. In many cases the aetiology of vasculitis is unknown; however, exposure to environmental agents such as infections or drugs is a known risk factor for hypersensitivity vasculitis[1]. Withdrawal of the offending agent may assist in diagnosis since symptoms usually subside upon exposure termination. IgA vasculitis, (formerly Henoch-Schönlein purpura), is a small vessel leukocytoclastic vasculitis with IgA-immune complex deposits in the vessel wall. While more common in children, it tends to induce severe disease in adults. IgA vasculitis presents mainly as a purpuric rash, abdominal pain and IgA nephropathy[2].

Purpura fulminans (PF) is a severe, life-threatening form of purpuric rash, involving extensive microvascular coagulation leading to ecchymosis, haemorrhagic bullae and skin and organ necrosis. This rare vasculopathy is underlined by decreased or dysfunction of protein C, protein S or antithrombin, mainly due to congenital protein C deficiency, severe sepsis or acquired disease[3]. Patients are often severely ill with fever, haemodynamic instability and haemorrhages. This rapid, frequently catastrophic event requires immediate diagnosis and treatment utilising supplementation of fresh frozen plasma, plasma exchange if an antibody-mediated process is suspected, or both. Despite the improvement of supportive care and management of secondary complications, the mortality rate remains high and disease outcomes remain poor, often requiring multiple amputations.

We present a patient who suffered a rare, life-threatening episode of IgA-mediated hypersensitivity vasculitis and purpura fulminans-like event.

CASE DESCRIPTION

A previously healthy 66-year-old man presented to his general practitioner with swelling of the second right-hand finger and was treated with naproxen 500 mg for three days. Four days afterwards, he developed a petechial rash on both feet and a fever up to 38.4°C *(Fig. 1A)*. His blood tests revealed new pancytopenia and acute kidney injury with a creatinine level of 1.5 mg/dl (normal range 0.67–1.17). He was treated with azithromycin 500 mg for 2 days for possible infection. Notably, at that point he reported a similar rash in the past, which appeared after taking an over-the-counter non-steroidal anti-inflammatory drug (NSAID) and subsided once therapy was aborted. On the sixth day while receiving azithromycin his rash evolved to a non-painful purpuric rash that spread rapidly across his limbs, torso and face. He was admitted to the hospital with extensive and fulminant skin necrosis of the extremities including fingers, nose and ears, alongside declining renal function, abdominal pain, haematochezia and bloody diarrhoea *(Fig. 1A)*. Due to uvular oedema and impending airway endotracheal, intubation was carried out and he was transferred to the ICU.

In the ICU, additional laboratory results revealed decreased levels of protein C, antithrombin, fibrinogen and C3 while D-dimer, creatinine and C-reactive protein (CRP) were elevated *(Table 1)*. Detailed infectious serology was negative

Figure 1. Clinical manifestations of purpura fulminans and outcomes: A, during hospitalisation; B, outcomes 3 weeks after discharge from the hospital. No amputations were required.

Variable	Reference range, adults	Upon admission to hospital	During ICU stay	Three weeks after discharge from hospital
White cell count K/µl	4.0–10.8	6.14	18.42	8.98
Neutrophils absolute (K/µl)	1.8–7.7	4.56	14.89	3.83
Lymphocytes absolute (K/µl)	1–4.8	1.09	2.29	2.29
Eosinophils absolute (K/µl)	0–0.5	0.05	0.00	0.07
Haemoglobin (g/dl)	13.5–17.5	13.19	9.48	9.56
Platelet count K/µl	130-440	140	165	194
Creatinine mg/dl	0.67–1.17	1.39	3.1	0.80
C-reactive protein mg/l	0–5	54.97	103.73	19.22
D-dimer ng/ml	0–500	20,135	58,328	7,397
Prothrombin time %	75–135	98	80	89
International normalised ratio	0.8–1.2	1.0	1.15	1.06
Fibrinogen mg/dl	200–400	207	109	231
Protein C %	85–150		42	100
Antithrombin %	80–135		57	
Complement C3 mg/dl	90–180		33.3	130
Complement C4 mg/dl	15–53			55
Anti-nuclear antibodies	negative		negative	
Anti-double stranded DNA	negative		negative	
Anti-proteinase 3 antibody	negative		negative	
Anti-myeloperoxidase antibody	negative		negative	
Anti-histone antibody	negative		negative	
Anti-neutrophil cytoplasmic antibody	negative		negative	

Table 1. Laboratory data

(including bacterial, viral, rickettsial and fungal). Extensive autoimmune serology was also non-contributing *(Table 1)*. Endoscopic examinations did not indicate a source of bleeding. Abdominal CT demonstrated multifocal thickening of the small and large bowel and luminal hyperenhancement. A skin biopsy showed dilated upper dermal capillaries with focal perivascular neutrophil infiltrates and nuclear dust. On direct immunofluorescence testing, a strong IgA sedimentation around vessel walls was documented.

Considering the dramatic presentation, rapid deterioration and the impending risk of organ loss and risk to the patient's life, a broad therapeutic approach was initiated including supportive therapy (e.g. hydration), a broad-spectrum antibiotic coverage with meropenem and doxycycline (until all cultures returned sterile), repeated plasma exchange with supplementation of fresh frozen plasma, anticoagulation followed by pulse dosing of methylprednisolone and later on, a gradual tapering of glucocorticoids.

The patient improved remarkably within days following plasma exchange and his skin rash continued to subside very gradually until complete resolution *(Fig. 1B)*. Notably, protein C and complement normalised in parallel to disease resolution *(Table 1)*.

DISCUSSION

IgA vasculitis involves deposition of immune complexes in blood vessel walls mainly in the skin, manifesting as purpura[2]. Triggers may include infections (e.g. IgA vasculitis – formerly Henoch-Schönlein purpura) or rarely, exposure to environmental factors such as drugs, inducing serum sickness and/or vasculitis with IgA-deposition[4–7]. Our patient's history suggests prior hypersensitivity to NSAIDs possibly causing severe sickness upon re-exposure. Thus, withdrawal of the drug and complete avoidance of NSAIDs re-exposure was recommended.

Another unique aspect is the fulminant rash presentation, pointing to the diagnosis of acquired purpura fulminans-like eruption. Congenital PF is related to very low levels of protein C, which were not observed here. However, acquired PF may present mildly, and normalisation of protein C levels is typical upon disease regression. Severe infection with gram-negative bacteria is the most common cause of acquired PF; nonetheless, exposure to NSAIDs or antibiotics was reported[8-10]. Other causes of acquired protein C deficiency such as vitamin K deficiency, warfarin therapy, hepatic failure, sepsis and chemotherapy were ruled out for our patient. Specific analysis for the inhibitors in this case

was not conducted due to test unavailability.

Although little evidence exists to guide clinical decision-making, urgent supportive care is imperative in the management of PF. Specific treatments include aggressive anticoagulation, repletion of protein C with FFP, activated protein C or protein C concentrate, or therapeutic plasma exchange with fresh frozen plasma replacement fluid[3].

In this case, the quick initiation of anticoagulation and FFP did not result in improvement. As protein C deficiency was moderated, autoimmune acquired PF was suggested and plasmapheresis was initiated followed by glucocorticoids. These interventions resulted in a quick and remarkable clinical response as well as normalisation of laboratory results including protein C levels.

Taking it all together, our patient's history suggests that re-exposure to NSAIDs may have triggered hypersensitivity IgA vasculitis and acquired protein C deficiency leading to a PF-like eruption. The calculated adverse drug reaction probability score (Naranjo) indicates that an adverse drug reaction is 'probable'[11]. Notably, re-exposure to NSAIDs was not feasible due to reaction severity and imminent risk to life. Early diagnosis, drug discontinuation and aggressive interventions resulted in the complete resolution of his condition.

This rare cross link between a commonly used drug (NSAID) and severe life-threatening hypersensitivity reactions requires a high index of suspicion for immediate diagnosis, long-term drug avoidance and early, aggressive interventions to avoid organ damage, amputations or death.

REFERENCES

1. Frumholtz L, Laurent-Roussel S, Lipsker D, Terrier B. Cutaneous vasculitis: review on diagnosis and clinicopathologic correlations. *Clin Rev Allergy Immunol* 2021 Oct;**61**:181–193.
2. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch-Schönlein purpura) in adults: diagnostic and therapeutic aspects. *Autoimmun Rev.* 2015 Jul;**14**:579–585.
3. Colling ME, Bendapudi PK. Purpura fulminans: mechanism and management of dysregulated hemostasis. *Transfus Med Rev* 2018;**32**:69–76.
4. Pillebout E, Sunderkötter C. IgA vasculitis. *Semin Immunopathol.* 2021 Oct;**43**:729–738.
5. Kelly BG, Stratton DB, Mansour I, Tanriover B, Culpepper KS, Curiel-Lewandrowski C. Navigating the initial diagnosis and management of adult IgA vasculitis: a review. *JAAD Int* 2022 Jun 13;**8**:71–78.
6. Rasmussen C, Tisseyre M, Garon-Czmil J, Atzenhoffer M, Guillevin L, Salem J-E, et al. Drug-induced IgA vasculitis in children and adults: revisiting drug causality using a dual pharmacovigilance-based approach. *Autoimmun Rev* 2021 Jan;**20**:102707.
7. Yousif M, Vigil NH, Haddad R. Drug-induced IgA vasculitis in an adult. *Cureus* 2023;**15**:e34270.
8. Chalmers E, Cooper P, Forman K, Grimley C, Khair K, Minford A, et al. Purpura fulminans: recognition, diagnosis and management. *Arch Dis Child* 2011;**96**:1066–1071.
9. Kosaraju N, Korrapati V, Thomas A, James BR. Adult purpura fulminans associated with non-steroidal anti-inflammatory drug use. *J Postgrad Med* 2011;**57**:145–146.
10. Alamri Y, Chua I, Douglas NM. A case of purpura fulminans attributed to trimethoprim-sulfamethoxazole. *N Z Med J.* 2023;**136**:72–76.
11. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–245.