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Amiodarone-induced cutaneous vasculitis. A different view of leukocytoclastic vasculitis and the reason physicians must be alert

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Abstract

We present a case of small vessel vasculitis happening immediately after starting treatment with amiodarone in a 75 year old female with End-Stage Kidney Disease (ESKD) due to chronic interstitial nephritis, on regular hemodialysis during the last five years. During a routine dialysis session, she complained of dizziness and palpitations, and found to have paroxysmal atrial fibrillation, with an irregular rhythm of 155 heart beats per minute. The patient was successfully treated with amiodarone administrated intravenously, at a dose of 1 mg/min for 6 hours followed by 0.5 mg/min for the next 18 hours. Treatment was continued orally, though 48 hours after the event, she developed a palpable purpuric rash with hemorrhagic blisters at the lower limbs. Skin biopsy was scheduled 24 hours later, showed leukocytoclastic vasculitis, mild edema, orthokeratosis, nuclear dust and infiltration of neutrophils, lymphocytes and few histiocytes.

Dermal vessels had severe inflammation with foci of fibrinoid necrosis and fragmented neutrophilic nuclei, findings consistent with drug induced leukocytoclastic vasculitis. Amiodarone was discontinued and she was commendably treated with steroids. Vasculitis is one of the less-reported side effect of amiodarone treatment, and this is the first described case in a dialysis patient. Physicians should be alert for the potential complication, which usually shows an abrupt response when directly treated.

Keywords

Disease; Dialysis; Atrial fibrillation; Heart beat; Skin.

Introduction

Amiodarone is one of the most commonly used antiarrhythmic drugs due to its high efficacy against supraventricular and ventricular cardiac arrhythmias [1]. Despite being associated with a variety of adverse effects, especially in cases of prolonged therapy, amiodarone often provides the last and most effective option to treat cardiac arrhythmias.

Antiarrhythmic agents, including amiodarone, have been associated with dermatological complications. Skin effects are not uncommon for amiodarone, which has been reported to cause phototoxic and photoallergic reactions, hyperpigmentation, pseudoporphyria, erythema nodosum and even toxic epidermal necrolysis [1].

A less common and rarely reported cutaneous side effect is amiodarone-induced vasculitis. We present a case of a 75-year-old woman with end-stage kidney disease (ESKD), who developed a purpuric rash, three days after the initiation of amiodarone treatment following a relapse of Atrial Fibrillation (AF) with rapid ventricular response.

Case Presentation

A 75-year-old female with End-Stage Kidney Disease (ESKD) due to chronic interstitial nephritis, being on Hemodialysis (HD) for the last five years, complained for palpitations, dysphoria and dizziness during her routine session. On examination her blood pressure was 130/85 mmHg with an irregular rhythm of 155 heart beats per minute and oxygen saturation levels on 98%. Heart auscultation revealed a rapid and irregularly cardiac rhythm, with the rest of physical examination being unremarkable. ECG revealed atrial fibrillation with rapid ventricular response and she was admitted for further investigation and treatment.

The patient had a known history of paroxysmal atrial fibrillation and was under treatment with Flecaidine 50 mg B.I.D. and Apixaban 2,5 mg B.I.D. Laboratory tests on admission are shown on Table 1.

A cardiology assessment was requested, and cardioversion was attempted according to the European Society of Cardiology (ESC) Guidelines. A loading dose of 150 mg amiodarone was administrated intravenously, followed by continuous administration of amiodarone in 1 mg/min for 6 hours and then 0.5 mg/min for 18 hours. Sinus rhythm was restored 24 hours after treatment initiation and no complications were noted.

Physical examination, vital signs, ECG and laboratory tests performed the day after, were unremarkable (Table 1).

Maintenance dose was decided to be continued orally, however 48 hours after the event, the patient developed a palpable purpuric rash of the lower limbs with hemorrhagic blisters (Figure 1). Amiodarone treatment was immediately discontinued and new laboratory assessment including immunological biomarkers was performed (Table 1).

Table 1: Laboratory investigation of the patient at presentation and during follow up.

	Admission	24 hrs after admission	48 hrs after admission (purpuric rash)	Normal Range
WBC	5100	8200	8900	4000-10000 x10^9 /L
HCT %	31.20%	31.30%	32%	36-47%
Platelets	303000	378000	376000	150000-450000
Creatinine	3.68	3.94	4,02	0.66-1.1 mg/dl
Urea	98	67	85	10-45 mg/dl
Sodium	135	136	138	136-145 meq/L
Potassium	5.7	4.5	5,1	3.5-5.2 meq/L
CRP	7	12	44	<6 mg/L
ESR	18		56	0-29 mm/hr
ANA (IFA)			POSITIVE 1/1280	NEGATIVE
ANTI-dsDNA (IFA)			NEGATIVE	NEGATIVE
ANTI-dsDNA (ELISA)			NEGATIVE	<25 IU/ml
MPO-ANCA (ELISA)			NEGATIVE	<5 U/ml
PR3-ANCA (ELISA)			NEGATIVE	<5 U/ml
Anti-ENA (ELISA)			NEGATIVE	<1 U/ml
C3			107	79-152 mg/dl
C4			23.2	16-38 mg/dl
IgM			117	46-304 mg/dl
IgG			1020	751-1560 mg/dl
IgA			450	82-453 mg/dl
RA-test			NEGATIVE	<20 IU/ml
Troponin I h.s.	13	12.9	14	<11.6 pg/ml
PT	10.6	10.9	10.6	sec
INR	0.91	0.94	0.93	0,85-1,15
APTT	26.8	31.4	29.3	sec
Fibrinogen	524	588	581	180-350 mg/dl
D-Dimmers	2329		1867	0-500 ng/ml
HBsAg			NEGATIVE	0,00-1,00 S/CO
Anti-HBS			POSITIVE	0,00-10,00 mIU/ml
HBeAg			NEGATIVE	0,00-1,00 S/CO
Anti-HBc-T			NEGATIVE	0,00-1,00 S/CO
HIV-Ag-Ab			NEGATIVE	0,00-1,00 S/CO
Anti-HCV			NEGATIVE	0,00-1,00 S/CO
CEA			4,3	<10 ng/ml
CA 19-9			26.1	<35,0 IU/ml
CA 125			14	<35 IU/ml
CA 15.3			19.,6	<23.5 IU/ml
A-Fetoprotein			4	<9.0 ng/ml

Skin biopsy was scheduled 24 hours after the appearance of the lesion, revealing histopathological features (Figure 2) indicative of Leukocytoclastic Vasculitis (LCV). The epidermis showed orthokeratosis and mild atrophy.

In the upper dermis there was mild edema, red blood cell extravasation, nuclear dust and inflammatory infiltrate composed of neutrophils, lymphocytes and few histiocytes.

There was inflammatory infiltrate in the wall of the dermal vessels with foci of fibrinoid necrosis and fragmented neutrophilic nuclei.

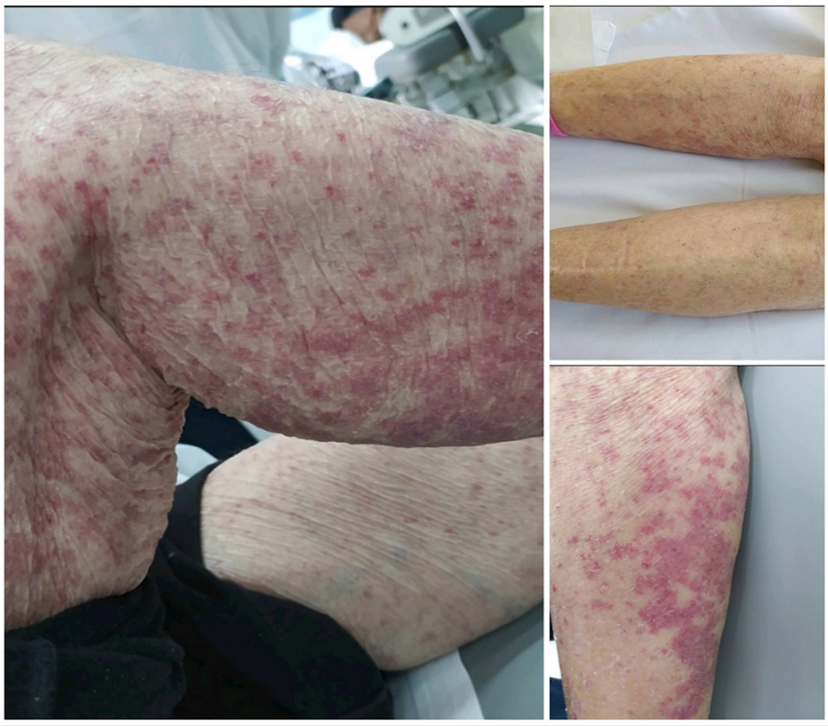

Figure 1: The palpable purpuric rash before (upper figure and bottom left) and after the treatment (bottom right).

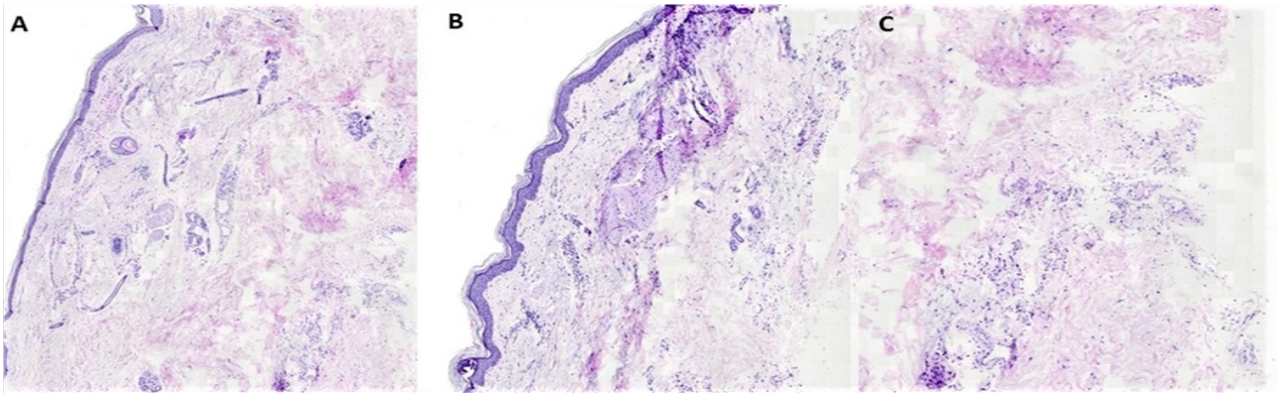

Figure 2: Skin biopsy: A. In low power magnification, the epidermis has no significant changes. In the dermis there is perivascular inflammation B. Higher power reveals busy dermis with RBC extravasation and mild-moderate inflammation around and in the wall of dermal vessels. Note the neutrophils, lymphocytes and few histiocytes of the infiltrate C. High power of the inflammatory infiltrate in the vessel wall and the nuclear dust of fragmented neutriphilic nuclei.

Discussion

Amiodarone is one the most commonly used antiarrhythmic medication. Physicians often encounter amiodarone's cutaneous adverse effects, as a result of the drug's widespread use [1].

The incidence of cutaneous side effects in patients with prolonged use of amiodarone is approximately 75% according to the literature and the most commonly encountered dermatological complications are photoallergic and phototoxic reactions, hyperpigmentation and pseudoporphyria. Most of these skin lesions, reverse after drug withdrawal [1].

The wide range of manifestations that amiodarone-related cutaneous reactions are presented, should be well-known to physicians, in order not to be underdiagnosed or mistreated.

One of the less reported cutaneous complications is amiodarone-induced vasculitis. Medicines, viral or bacterial infections, autoimmune disorders and malignant diseases are the most common causes of Leukocytoclastic Vasculitis (LCV) and its main clinical manifestation is a palpable purpuric rash [2]. The lesion usually appears on the lower limbs and buttocks and it is usually bilateral. The estimated time between triggering event and the appearance of the rash is about one to three weeks [3].

LCV is a small vessel vasculitis and is diagnosed exclusively with skin biopsy with direct Immunofluorescence (IF). Light microscopy will reveal inflammatory cells around small vessels causing wall destruction and necrosis. Infiltrating leucocytes consists of lymphocytes or neutrophils are usually degenerated, a finding described as "leukocytoclasis with nuclear dust," also known as "karryorrhexis". Another common finding in skin biopsy regarding drug-related LCV, is the presence of eosinophils in the dermis [3]. Direct immunofluorescence is characterized by immune-complex deposition of the dermal capillaries and venules, indicating that LCV is an immune-complex mediated vasculitis, restricted to cutaneous vessel, affecting both arterioles and veins.

LCV usually does not require aggressive therapy. Conservative approach such as compressions, leg elevation and antihistamines are often effective and in cases of drug-induced LCV, drug withdrawal is essential. If hemorrhagic blisters or indications of skin necrosis are present, corticosteroids must be administrated orally with fast tapering otherwise they can be harmful especially in children. Systemic administration of corticosteroids must only be considered in cases of severe systemic involvement [4]. Immunosuppressive steroid-sparing agents are rarely needed.

Although LCV is often manageable and treatable with mild measures, all physicians who are treating such a patient must me alert. LCV can conceal severe underline disease therefore physical examination and complete laboratory tests must be performed. Leukocytoclastic vasculitis may be the first manifestation of a severe disease therefore finding and treating the underlying cause can be lifesaving.

A variety of infections have been associated with LCV in the past. Covid-19, HIV, chronic HBV, Streptococcal infection, Mycobacterium, Staphylococcus aureus, Neisseria are only some of the infectious triggers that can stimulate immune mechanisms and potentially lead to LCV. Detailed medical history, full body

examination and special laboratory and radiological examinations must be performed in case the physician suspects an underlying infection. In rare cases, LCV can be a result of sepsis therefore infections must always be considered as a triggering factor [5].

Besides infections, autoimmune disorders can also cause secondary leukocytoclastic vasculitis such as Systemic Lupus Erythematosus, Rheumatoid Arthritis, Henoch-Schonlein Purpura and Behcet Disease. Considering that autoimmune disorders can be presented with a variety of manifestations, immunological biomarkers must be included in the laboratory tests if suspected [6].

Malignancy is another contributing factor a physician must have in mind when encountering LCV. In rare cases hematologic malignancies such as lymphomas or some types of leukemia but also in other types of cancer as well including lung and intestinal cancer, can be triggers of secondary LCV. Chest X-ray or CT scan, tumor markers and endoscopy may be diagnostic in cases like those mentioned above [8].

Regarding drug-induced cutaneous vasculitis like our case reported above, drugs are indeed the "usual suspect" when LCV occurs. Several drugs have been associated with secondary leukocytoclastic vasculitis. These include but not limited to, anti-arrhythmic drugs such as amiodarone, antibiotics such as beta-lactams, vancomycin, clindamycin or erythromycin, diuretics like furosemide and thiazides, allopurinol, phenytoin, warfarin, metformin among many others [4]. In most cases as mentioned before, drug withdrawal is enough to reverse the cutaneous manifestation. Although a drug may be the obvious cause of LCV, every other possible cause must be included in our differential diagnosis because the life of our patient may depend on it [1-4].

As mentioned above, a variety of cutaneous manifestations related to amiodarone along with the possible mechanisms that these skin complications are connected with, have been well-described and reported.

The mechanism of phototoxic and photoallergic reactions is believed to be through the creation of active metabolites such as oxygen free radicals, leading to destruction of DNA particles, cell membranes, and oxygenation of lipids [1].

Regarding hyperpigmentation, although the exact mechanism is not fully understood, histopathological examination suggests that depositions of lipofuscin aggregates within macrophages, mast cells, endothelial cells, fibrinoblasts and other cells, lead to the characteristic skin discoloration of amiodarone [1].

Pseudoporphyria, IgA Bullous Dermatosis, dermatitis herpetiformis, psoriasis erythema nodosum and toxic epidermal necrolysis are also some of the adverse reactions that amiodarone is also reported to be connected with, but the mechanisms by, these reactions occur, are not precisely described [1].

Amiodarone-induced vasculitis is one of the less-reported cutaneous side effect of amiodarone administration. There are less than ten cases reported in the medical literature but it is not yet clarified if this entity is indeed rare or just underdiagnosed [9]. Most of those cases, as reported, were treated conservatively.

In our case presented above, it is important to note that this is the first case of amiodarone-induced vasculitis that occurs in a patient being on hemodialysis. The presence of hemorrhagic blisters was an indication for pharmaceutical intervention instead of a conservative approach.

Although the patient responded well to corticosteroids, it is important for every physician encounters cases like this, to fully investigate for other possible causes of leukocytoclastic vasculitis that can be severe and life threatening.

Conclusion

Histological findings consistent with leukocytoclastic vasculitis, probably related, in relation to the medical history, with drug reaction.

The patient received treatment with corticosteroids, methylprednisolone of 16 mg per day for one week, followed by gradual tapering by 4 mg/week, presenting gradual improvement until complete recession of the rash, 14 days after the initial event (Figure 1).

Despite the absence of systemic involvement indication an extensive workup was performed anyway to exclude the possibility of potential infection, systemic disease or malignancy associated with LCV. None of the tests including immunological biomarkers, chest X-ray and tumor markers, indicated any other cause of LCV therefore amiodarone-induced cutaneous vasculitis was our most probable diagnosis.

Moderate inflammation around and in the wall of dermal vessels. Note the neutrophils, lymphocytes and few histiocytes of the infiltrate C. High power of the inflammatory infiltrate in the vessel wall and the nuclear dust of fragmented neutriphilic nuclei.

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References

1. Jaworski K, Walecka I, Rudnicka L, Gnatowski M, Kosior DA. Cutaneous adverse reactions of amiodarone. Med Sci Monit. 2014; 20: 2369-2372.

2. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. Intern Emerg Med. 2021; 16: 831-841.

3. Baigrie D, Goyal A, Crane JS. Leukocytoclastic Vasculiti. In: StatPearls. Treasure Island: StatPearls Publishing; 2022.

4. Sunderkötter C, Bonsmann G, Sindrilaru A, Luger T. Management of leukocytoclastic vasculitis. J Dermatolog Treat. 2005; 16: 193-206.

5. Goeser MR, Laniosz V, Wetter DA. A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol. 2014; 15: 299-306.

6. Ooi JD, Deng J, De Souza AWS. Editorial: Autoimmune Vasculitis - Advances in Pathogenesis and Therapies. Front Immunol. 2021; 12: 720257.

7. Ak T, Algan RN, Agirgol S, Hascicek SO, Turkoglu Z. Amiodarone-induced cutaneous leukocytoclastic vasculitis: A case report and a review of the literature. Clin Rheumatol. 2022.

8. Heijl C, Westman K, Höglund P, Mohammad AJ. Malignancies in Patients with Antineutrophil Cytoplasmic Antibody-associated Vasculitis: A Population-based Cohort Study. J Rheumatol. 2020; 47: 1229-1237.

9. Ndiaye M, Lebrun-Vignes B, Ortonne N, Fardet L. Vascularite cutanée induite par l'amiodarone [Amiodarone-induced immune complex cutaneous vasculitis]. Ann Dermatol Venereol. 2017;144: 788-792.

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