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Hydroxychloroquine-induced Sweet's Syndrome: A Case Report and Literature Review

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Sweet's syndrome (or acute febrile dermatosis) is a neutrophilic dermatosis with a characteristic presentation encompassing specific clinical (fever and erythemato-violaceous oedematous papules, plaques and nodules), laboratory (neutrophilia and increased inflammatory markers), and histological (dermal neutrophilic infiltrate without vasculitis) features. Its pathophysiology is poorly understood but there seems to be an auto-inflammatory component related to mutations in inflammasome genes. It has been subdivided into its classic form, malignancy-associated, and drug-induced, according to its aetiology. The condition usually responds rapidly to steroid therapy, but recurrences are common. This report presents an extremely rare case of hydroxychloroquine-induced Sweet's syndrome, plus a review of the literature, which encompasses 3 previous cases of Sweet's syndrome induced by hydroxychloroquine and 1 induced by chloroquine. Despite being relatively easy to diagnose, aetiological investigation poses challenges to the clinician, especially in the elderly population, as several confounding factors might be present. Further studies are necessary to shed light on the pathophysiology behind this entity, to further facilitate diagnostic workup and treatment strategies.

Key words: Sweet; hydroxychloroquine; chloroquine; drug-induced; neutrophilic.

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Sweet's syndrome (or acute febrile neutrophilic dermatosis) is one of the neutrophilic dermatoses, alongside pyoderma gangrenosum and subcorneal pustular dermatosis, among others. Despite being clinically heterogeneous, all these conditions exhibit intense neutrophilic infiltrate on histopathological examination. This entity is usually sub-grouped into (*i*) classic form (which encompasses idiopathic cases as well as those associated with either infections, vaccination, pregnancy, or inflammatory bowel disease), (*ii*) malignancy-associated (more frequently related to haematological malignancies), and (*iii*) drug-induced (1–6).

SIGNIFICANCE

Dermatological conditions (for example, Sweet's syndrome) may be behind many more serious systemic diseases but may also be due to adverse drug reactions. It is complex to distinguish among all possible causes and we present some insight that might be helpful in doing so. Furthermore, we present some very rare cases of hydroxychloroquine-induced Sweet's syndrome and review all previously reported cases. Our work is important to heighten awareness and improve the diagnosis and investigation of this condition.

To our knowledge there have only been 3 previously reported cases of hydroxychloroquine-induced Sweet's syndrome (7, 8).

CASE REPORT

We report the case of a 71-year-old Brazilian man, who came to our walk-in emergency dermatology clinic with a 3-day history of widespread erythemato-violaceous papulonodules and plaques on the face, upper and lower limbs, and the trunk. He also reported fever (38.5ºC) and mentioned he had re-started therapy with hydroxychloroquine about a week before the onset of the symptoms. There was no history of previous infection or vaccination.

He mentioned similar symptoms 2 months previously, about 2 weeks after he had first been prescribed hydroxychloroquine for arthralgias. However, at that time, he discontinued hydroxychloroquine and took over-the-counter hydroxyzine 25 mg, which resulted in remission of the lesions.

The patient's medical history was relevant for HIV-1 infection since 1995, for which he was treated with dolutegravir/rilpivirine and had had an undetectable viral load for several years. His latest CD4 count showed 405 cells/μL. He also had a history of pancytopenia and hand arthralgias due to chronic parvovirus B19 infection (persistently positive viral loads on PCR tests).

On examination dozens of tumid oedematous and erythemato-violaceous plaques and nodules were seen, gradually coalescing to form small to medium, irregular, sharply bordered, oedematous plaques, some with a vesicle-like appearance in the centre. They were symmetrically distributed on his arms, forearms, neck, back, and face (**Fig. 1**).

Complete blood count revealed neutrophilia (85.1%) without leucocytosis (9.2×10^9/L) and increased inflammatory markers (ESR 120 mm/h and CRP 8.99 mg/dL). To rule out neoplasm and infection, a full blood panel was performed, including blood cultures, viral serologies, and immunofixation, and the results were unremarkable. He underwent full-body computed tomography, which identified no tumours.

Skin biopsies were performed, and histopathological examination later showed normal epidermis but revealed neutrophilic

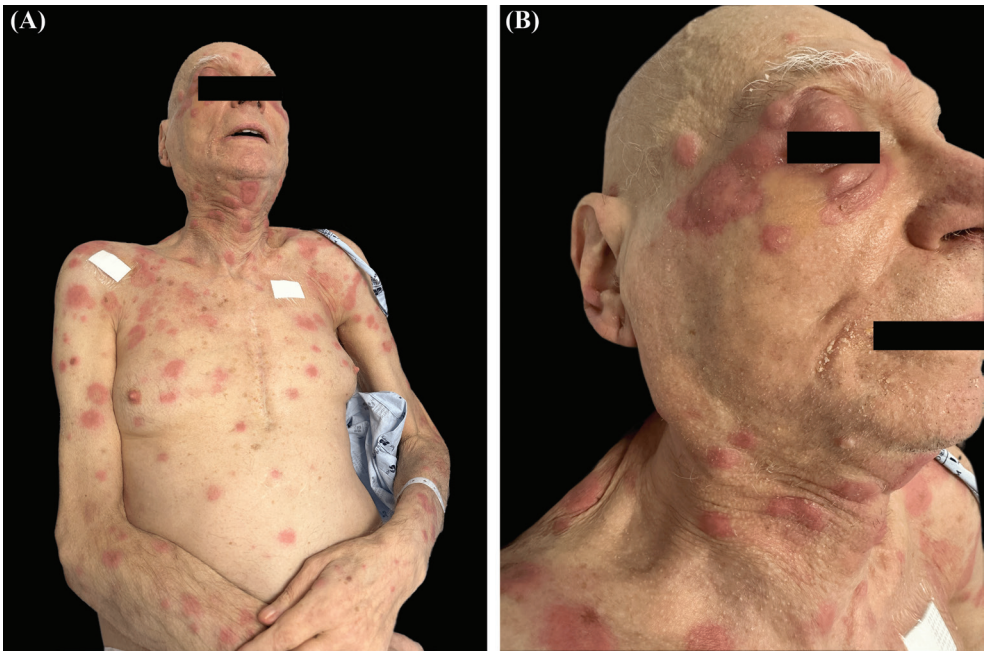

Fig. 1. Clinical pictures: erythemato-violaceous papules, nodules and plaques on (A) upper body and (B) face.

inflammatory infiltrate, both interstitial and perivascular, in the superficial dermis. It also showed capillary ectasia around the papillary dermis but displayed no signs of vasculitis. These finds were consistent with Sweet's syndrome (**Fig. 2**).

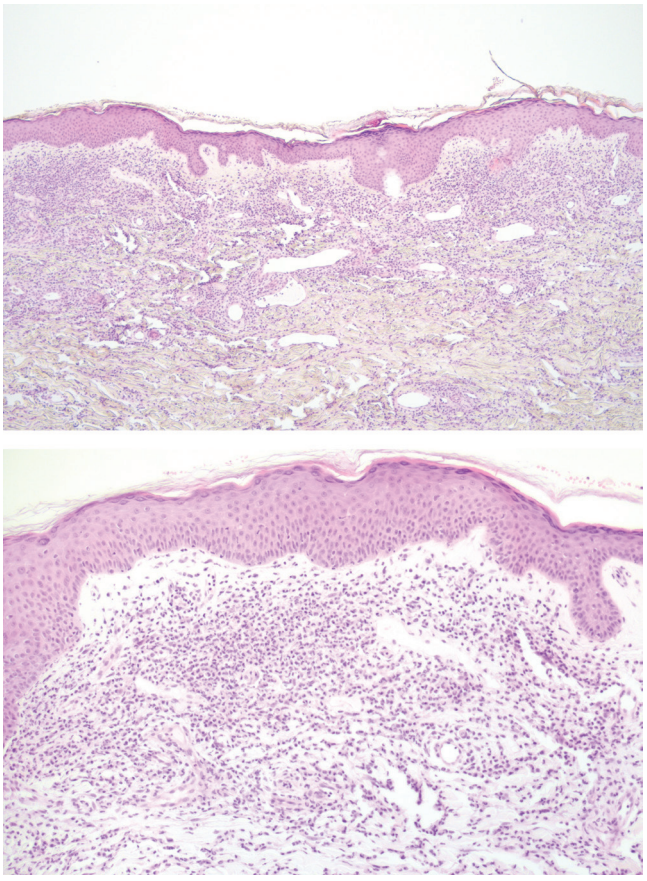

Fig. 2. Histopathological findings: neutrophilic inflammatory infiltrate in the upper dermis without vasculitis, papillary dermal oedema, dense diffuse and perivascular neutrophilic infiltrate, dilation of blood vessels.

The patient was started on prednisolone 20 mg/day, hydroxychloroquine was withdrawn, and the lesions remitted almost completely within 1 week.

A final diagnosis of Sweet's syndrome was made, as our patient fulfilled 2 major and 3 minor criteria, as defined by Von den Driesch in 1994 (9).

LITERATURE REVIEW

In 2019, Bodard et al. (7) reported 2 cases of patients who developed Sweet's syndrome following therapy with hydroxychloroquine for lupus erythematous and Sjögren's syndrome, respectively. In the same year, Manzo et al. (8) reported 1 case of hydroxychloroquine-induced Sweet's syndrome in a patient with Sjögren's syndrome. Interestingly, as happened in our case, Manzo's patient also experienced Sweet's manifestations twice after a drug rechallenge was attempted. A similar scenario was previously described by El Moutaoui et al. (10) in 2009, the only report of chloroquine-induced Sweet's syndrome describing a similar drug re-challenge scenario (**Table I**).

DISCUSSION

Despite having a typical clinical presentation, the aetiological investigation of Sweet's syndrome may prove challenging, especially in the elderly population, as these patients typically have more comorbidities and are polymedicated. Thorough review of systems is mandatory and, especially in the setting of immunosuppression, workup should include exclusion of underlying neoplasm (11, 12).

Some authors have considered HIV to be a risk factor for Sweet's syndrome. Several mechanisms have been

Table I. Sweet's syndrome and hydroxychloroquine/chloroquine: case reports in indexed literature

Case reports	Year of publication	Offending drug	Underlying disease	Sweet's syndrome criteria	DISS criteria
Bodard et al. (7) (2 cases)	2019	Hydroxychloroquine	SS	2 major+2 minor	5/5
			SLE	2 major+2 minor	5/5
Manzo et al. (8)	2019	Hydroxychloroquine	SS	2 major+3 minor	5/5
El Moutaoui et al. (10)	2009	Chloroquine	SLE	2 major+3 minor	5/5

considered, namely neutrophilic chemotaxis in relation to a hypersensitivity reaction (13, 14), compromised T-helper lymphocytic function (15, 16), or HIV transactivating proteins (17), but no consensus has been reached. A review by Mudroch et al. (12) found most cases of Sweet's syndrome reported in HIV-positive patients had other causes, namely immune reconstitution inflammatory syndrome in 25% of cases, AIDS-defining conditions, infections, and drugs. Although there have been some case reports of Sweet's syndrome as an initial presentation of HIV (13, 17), others merely hypothesize HIV to be the causative agent after other aetiologies have been ruled out. None of the published cases suggest a link between Sweet's syndrome and CD4 cell count, viral load, or disease duration (18–21). In our case, the fact that the patient presented the symptoms on 2 different occasions following the introduction of 1 drug and the fact that he had been HIV positive for over 20 years and had undetectable viral load seems to favour another aetiology.

Drug-induced Sweet's syndrome is a rare entity. It is estimated that drug-induced Sweet's syndrome accounts for less than 10% of all cases of Sweet's syndrome (22, 23). A French study from 2023 found only 136 cases out of 994,789 adverse drug reaction events reported in a pharmacovigilance database. The most frequently reported offenders were bortezomib, azacitidine, pegfilgastrim, azathioprine, and bendamustine (24).

In 1996, Walker and Cohen (25) outlined specific criteria for drug-induced Sweet's syndrome, which the patient in our case fulfilled entirely (**Table II**).

When the Naranjo score (26) was applied, our patient scored 9, which considers the drug as definitely having caused the adverse drug reaction.

In conclusion, this case report highlights a rare instance of hydroxychloroquine-induced Sweet's syndrome, adding to the limited body of literature on drug-induced Sweet's syndrome. The pathophysiology underlying this adverse reaction remains incompletely understood but may involve a hypersensitivity mechanism, immune dysregulation, or direct toxic effect on neutrophils. In recent years, Sweet's syndrome has been categorized as an auto-inflammatory disease, which means that mutations in inflammasome genes might play a role in perpetuating recurrent inflammation despite the absence of circulating antigens (27–32). It is most frequently associated with colony-stimulating factors or cytostatic drugs, although many other associations have been described before (33). To our knowledge, it is the 4th published case establishing the association between hydroxychloroquine and Sweet's syndrome and the first reporting a patient who did not have an autoimmune connective tissue disease.

Further studies and case reports are needed to better understand the incidence and mechanisms, and thus ameliorate diagnostic workup and management strategies. By documenting this case, we hope to provide valuable insights for healthcare providers, enhancing their ability to diagnose and manage similar cases effectively.

Table II. Diagnostic criteria for Sweet's syndrome (classic form and drug-induced)

	Classic	Drug-induced
Major	Abrupt onset of tender erythematous plaques/nodules	
Major	Neutrophilic infiltrate of the dermis without vasculitis	
Minor	Fever >38.0ºC	
Minor	Previous infection or vaccination, pregnancy, malignancy, or inflammatory disease	Temporal relation between drug initiation and onset of dermatosis
Minor	ESR >20, positive CRP, leucocytosis >8,000, neutrophils >7,000 (≥3)	Remission of symptoms after drug discontinuation or steroid therapy
Minor	Rapid response to steroid therapy	
Diagnosis requires	2 major + ≥2 minor	All 5 criteria

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Data availability: The data used to support the findings of this study are available from the corresponding author upon request.

The authors have no conflicts of interests to declare.

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