Unfractionated heparin (UFH) is frequently used in the treatment of venous thromboembolism and acute coronary syndrome. There are many common cutaneous adverse reactions to this medication. We present a unique case of hemorrhagic bullae limited to the oral mucosa that developed within 6 hours of a patient receiving UFH.

Heparin is a naturally occurring anticoagulant and is commonly used to treat or prevent venous thrombosis or the extension of thrombosis. Heparin is composed of 15-kDa chains of complex polysaccharides with repeating pentasaccharide sequences. These high-affinity pentasaccharide subunits bind and activate antithrombin III, which exerts its dominant anticoagulant effects through the inhibition of factor Xa.

Adverse effects of heparin administration include bleeding, injection-site pain, and thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is a serious side effect wherein antibodies are formed against platelet antigens and predispose the patient to venous and arterial thrombosis. Dermatologic adverse effects of heparin range from commonly reported injection-site eruptions to the more rarely described distant or generalized cutaneous reactions.

Bullous hemorrhagic dermatosis is a poorly understood idiosyncratic drug reaction characterized by tense, blood-filled blisters that arise following the administration of subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin (UFH). First reported in 2006 by Perrinaud et al, only a few case reports describing this phenomenon exist in the literature.

We report a unique case of hemorrhagic bullae limited to the oral mucosa.

Case Report
An 84-year-old man was admitted to the cardiology service with severe substernal chest pain. An electrocardiogram did not show any ST-segment elevations; however, he had elevated troponin T levels. He had a medical history of coronary artery disease complicated by myocardial infarction (MI), as well as ischemic cardiomyopathy, hypertension, hyperlipidemia, ischemic stroke, and pulmonary embolism for which he was on long-term anticoagulation for years with warfarin, aspirin, and clopidogrel. The patient was diagnosed with a non–ST-segment elevation MI. Accordingly, the patient’s warfarin was discontinued, and he was administered a bolus and continuous infusion of UFH. He also was continued on aspirin and clopidogrel. Within 6 hours of initiation of UFH, the patient noted multiple discrete swollen lesions in the mouth. Dermatology consultation and biopsy of the lesions were deferred due to acute management of the patient’s MI.

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Physical examination revealed a moist oral mucosa with 7 slightly raised, hemorrhagic bullae ranging from 2 to 7 mm in diameter (Figure, A and B). One oral lesion was tense and had become denuded prior to evaluation. Laboratory testing included a normal platelet count (160,000/µL), a nearly therapeutic international normalized ratio (1.9), and a partial thromboplastin time that was initially normal (27 seconds) prior to admission and development of the oral lesions but found to be elevated (176 seconds) after admission and initial UFH bolus.

Upon further questioning, the patient revealed a history of similar oral lesions 1 year prior, following exposure to subcutaneous enoxaparin. At that time, formal evaluation by dermatology was deferred due to the rapid resolution of the blisters. Despite these new oral lesions, the patient was continued on a heparin drip for the next 48 hours because of the mortality benefit of heparin in non-ST-segment elevation MI. The patient was discharged from the hospital on a regimen of aspirin, warfarin, and clopidogrel. At 2-week follow-up, the oral lesions had resolved (Figure, C and D).

Comment

*Heparin-Induced Skin Lesions*—The 2 most common types of heparin-induced skin lesions are delayed-type hypersensitivity reactions and immune-mediated HIT. A 2009 Canadian study found that the overwhelming majority of heparin-induced skin lesions are due to delayed-type hypersensitivity reactions. The majority of these reactions occurred at or near the injection site on the abdomen and presented as eczematous plaques. Distant cutaneous involvement and lesions of the buccal mucosa were not as commonly reported. Female sex, obesity, and heparin treatment exceeding 9 days were identified as risk factors in the development of delayed-type hypersensitivity reactions, but our patient did not have any of these risk factors.

*Types of HIT*—Heparin-induced thrombocytopenia is one of the most serious adverse reactions to heparin administration. There are 2 subtypes of HIT, which differ in their clinical significance and pathophysiology. Type I HIT is a non-immune-mediated reaction that results from the direct effect of heparin on platelets, which causes platelet aggregation and thrombocytopenia. It presents within the first 2 days after heparin exposure. Type II HIT is an immune-mediated response caused by the formation of IgG autoantibodies against the heparin–platelet factor 4 complex. Antibody formation and thrombocytopenia typically occur after 4 to 10 days of heparin exposure, and there can be devastating arterial and venous thrombotic complications.

*Diagnosis of HIT*—Heparin-induced thrombocytopenia should be suspected in patients with a lowered platelet count, particularly if the decrease is more than 50% from baseline, and in patients who develop stroke, MI, pulmonary embolism, or deep vein thrombosis while on heparin. Heparin-induced thrombocytopenia was not observed in our patient, as his platelet count remained stable between 160,000 and 164,000/µL throughout his hospital stay and he did not develop any evidence of thrombosis.

*Differential Diagnosis*—Our patient’s lesions appeared morphologically similar to angina bullosa haemorrhagica, but this condition was less likely based on other clinical features. Typically, angina bullosa haemorrhagica appears as a solitary, blood-filled blister due to oral mucosal trauma from the ingestion of hard or abrasive food. Angina bullosa haemorrhagica most often is located on the soft palate because of its susceptibility to injury during mastication, and this lesion tends to be painful. In contrast, our patient developed 7 painless lesions on the buccal mucosa, sparing the soft palate, and without any history of preceding trauma.
Bullous pemphigoid also was considered given the presence of tense bullae in an elderly patient. However, the rapid and spontaneous resolution of these lesions with complete lack of skin involvement made this diagnosis less likely.  

**Heparin-Induced Bullous Hemorrhagic Dermatosis—** Because our patient described a similar reaction while taking enoxaparin in the past, this case represents an idiosyncratic drug reaction, possibly from antibodies to a heparin-antigen complex. Heparin-induced bullous hemorrhagic dermatosis is a rarely reported condition with the majority of lesions presenting on the extremities.

**Conclusion**

We describe a rare side effect of heparin therapy characterized by discrete blisters on the oral mucosa. However, familiarity with the spectrum of reactions to heparin allowed the patient to continue heparin therapy despite this side effect, as the eruption was not life-threatening and the benefit of continuing heparin outweighed this adverse effect.

**REFERENCES**