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Fat Necrosis of the Breast Associated with Anticoagulant Use: A Case Report

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Abstract

Breast necrosis is a rare complication of the use of anticoagulants. The few reports in the literature are mostly related to the use of warfarin. In general, treatment is conservative; however, surgical debridement may be required, and, less commonly, a mastectomy may be necessary. In the present case, not only was breast necrosis induced by anticoagulant use, but the drug in question was a direct thrombin inhibitor and the condition progressed to an advanced/severe stage. This article reports on a 64-year-old Brazilian woman who presented with breast necrosis following treatment for pulmonary thromboembolism with the new anticoagulant agent dabigatran. The advanced stage of the necrotic process required a mastectomy. The patient was discharged from hospital in a good state of health and in preventive use of the anticoagulant rivaroxaban. Since then, the patient has been followed up every six months with no complications being recorded. Direct thrombin inhibitors (the anticoagulant class of dabigatran) and direct factor Xa inhibitors (rivaroxaban) are now widely used as oral anticoagulants. Among the known adverse events of dabigatran, the occurrence of hematomas is described as infrequent and the likelihood of skin necrosis is not listed. This report highlights that the use of anticoagulants, either warfarin-based or thrombin inhibitors, represents a risk factor for skin necrosis. Treatment of this complication involves discontinuing the anticoagulant and later substituting the drug for one of another class. When the clinical presentation is more aggressive, more invasive treatment measures may be required and a differential diagnosis has to be made with malignant conditions.

Keywords: Fat necrosis; Breast; Anticoagulants; Thrombin inhibitors

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Abbreviations

POEMS syndrome: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes syndrome

Introduction

Fat necrosis of the breast was first described in 1920 by Hadfield as a benign, non-suppurative inflammatory process in adipose tissue. It most commonly affects women in the fourth to fifth decades of life. The condition was defined as an innocuous lesion of the breast presenting as a solid, firm tumor affixed to the skin that could be misdiagnosed as cancer [1].

The principal etiological cause is local trauma, which corresponds to 20% to 70% of cases. Other known factors are previous radiotherapy, use of anticoagulants, breast biopsies, breast-conserving surgery, reduction mammoplasty and lipofilling, with even less common causes including polyarteritis nodosa, Weber-Christian disease and granulomatous angiopanniculitis of the breast. Finally, in some patients, the etiology may remain unknown [1].

Case and Methods

A 64-year-old patient living in São Paulo, Brazil presented with a hematoma on her left breast that progressed to diffuse hardening of the whole breast associated with skin necrosis. The

onset of symptoms occurred two weeks after initiating use of the oral anticoagulant dabigatran etexilate mesylate (Pradaxa®). The medication was administered at the appropriate dose of 150 mg every 12 h for the treatment of pulmonary embolism. The patient's medical history included multiple myeloma, chronic arterial hypertension, type 2 diabetes mellitus and hypothyroidism. Currently, the patient is in use of rivaroxaban (Xarelto®; an oral factor Xa inhibitor) 10 mg/day for the prevention of thromboembolic disease, as well as levothyroxine, valsartan (Diovan®) and nifedipine.

The general status of the patient at admission to hospital was good, with no clinical history of fever and no cardiorespiratory abnormalities. Hyperemia was found to affect two-thirds of the left breast, together with a hematoma that included a necrotic lesion partially affecting the nipple-areola complex and lateral quadrants of the breast.

An abnormal mammogram classified as BI-RADS 4 showed diffuse cutaneous thickening and a diffuse increase in the density of the left breast. Ultrasonography of the breast revealed a mass with poorly defined contours in the central region of the left breast measuring 13.5 cm × 7.5 cm × 12.3 cm, with breast density distribution being classified as BI-RADS B4. The patient underwent core biopsy, with pathology revealing fat necrosis.

The condition progressed to hardening and petrification of the left breast; hence mastectomy of the left breast was required. At histopathology, macroscopic examination of the surgical specimen showed a yellowish-white mass measuring 15.0 cm × 10.0 cm × 5.0 cm with lobulated contours and firm consistency. Microscopic analysis revealed the presence of lymphohistiocytic infiltrate associated with necrosis of adipocytes and interstitial fibrosis. The surgical specimen tested negative for acid-fast bacillus, fungi and amyloidosis. The final diagnosis was fat necrosis. The patient was discharged in a good state of health and in use of rivaroxaban for the prevention of thromboembolic disease. She has been followed up at 6-monthly intervals and no complications have been recorded.

The institution's internal review board approved the publication of this case report. Informed consent and permission to publish were also obtained from the patient.

Discussion

Fat necrosis is a rare complication of anticoagulant use, with the breast being the site affected in 10% to 15% of cases [1,2]. In general, most necrotic lesions appear in areas with a large amount of subcutaneous tissue and are more common in women than in men [2-4].

Breast fat necrosis specifically resulting from the use of anticoagulants was first described in 1943. Since then, the condition has been the subject of fewer than 40 case reports, most of which involved an association with warfarin. In some cases, an association has been found with protein S and protein C deficiency [3], which are components of the natural anticoagulant system in the body. However, that was not the case here, since the patient had 85% of protein C activity and 80% of free protein S activity, both of these measurements being normal. In around 90% of cases, the painful necrotizing lesion appears on the third to sixth day after initiating anticoagulant treatment. The first sign is erythema of the breast skin, which may progress to irregular-appearing *peau d'orange* skin, then quickly to ecchymosis resulting from small hemorrhagic infarcts and ultimately to dry necrosis [3]. In all the different phases of the lesion, from early to advanced stages, or even when the condition is associated with a secondary infection of the tissue, diagnosis can be difficult. Furthermore, some cases may mimic inflammatory carcinoma of the breast, with an early biopsy being decisive in ruling out this possibility.

With the advent of new anticoagulants such as direct thrombin inhibitors, the occurrence of hematomas and skin necrosis should be taken into consideration as possible complications, although these events have been described as infrequent. Currently, direct thrombin inhibitors and direct factor Xa inhibitors are widely used as oral anticoagulants. The drug used by the patient in the case reported here was dabigatran, which is a direct thrombin inhibitor. According to the pharmacological properties of the drug, the occurrence of hematomas is described as infrequent and the likelihood of skin necrosis is not given. Vu and Gooderham described the occurrence of skin necrosis in patients using oral direct thrombin inhibitors. According to those authors, this adverse drug reaction is induced by the accumulation of the drug in the cutaneous tissue and is a rare event [4].

The initial treatment of fat necrosis in the breast is conservative and consists of clinical support following diagnosis. However, surgery may become necessary and may range from area debridement to mastectomy in the most severe cases such as the one described here [3]. In certain cases, fat necrosis may mimic inflammatory carcinoma of the breast and a biopsy may be required to rule out malignancy. A differential diagnosis of the patient described here would include multiple myeloma as well as the Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes (POEMS) syndrome. However, skin involvement, present in 65% of the patients affected by the POEMS syndrome, tends to present together with findings such as skin hyperpigmentation, hypertrichosis, acrocyanosis, plethora and hemangioma/telangiectasia [5].

The etiology of fat necrosis remains largely unknown and could be multifactorial. Local factors such as fluctuating temperature, trauma and inadequate tissue perfusion should be considered. The use of anticoagulants, either warfarin-based or thrombin inhibitors, represents a risk factor for skin necrosis as an adverse drug reaction. Treatment of this complication involves discontinuing the anticoagulant and later substituting the drug for one of another class. When the clinical presentation is more aggressive, more invasive treatment measures may be required and a differential diagnosis has to be made with malignant conditions.

As a single case report, there are inherent limitations associated with this paper. Notwithstanding, the strongpoint of this article lies in the description of an uncommon case of breast necrosis induced by the use of dabigatran, a new generation anticoagulant, rarely described in the literature. Moreover, the condition developed within a context of multiple myeloma in which other diagnostic hypotheses, such as breast amyloidosis, were evaluated.

Conclusion

The case reported here describes the diagnosis of fat necrosis of the breast in a patient undergoing treatment for pulmonary thromboembolism with the new anticoagulant agent dabigatran. Few cases of breast necrosis induced by anticoagulants have been reported, with most being warfarin-associated. This report highlights the relevance of monitoring the use of anticoagulants, either warfarin-based or thrombin inhibitors, as drugs that represent a risk factor for

skin necrosis. In the present case, the severe adverse drug reaction resulted in the need for mastectomy.

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