Cases have been described in newborns in the context of intrauterine infections and hematologic disorders. In adults, it can be associated with myelodysplastic and myeloproliferative syndromes, namely, disorders with ineffective or excessive hematopoiesis due to the formation of a neoplastic clone derived from an abnormal hematopoietic stem cell.

The processes most commonly associated with cutaneous extramedullary hematopoiesis are chronic myeloproliferative syndromes, in particular idiopathic myelofibrosis. It has been anecdotally associated with other entities, such as pachydermoperiostosis, pilomatrixoma, hemangioma, and even after administration of interleukin 3 by subcutaneous injection.

We describe the case of a patient with a history of idiopathic myelofibrosis.
myelofibrosis who, after 9 years, developed cutaneous lesions with histologic findings consistent with foci of cutaneous extramedullary hematopoiesis.

Case Description

A 55-year-old woman consulted in November 2005 for 2 nodules, one that had appeared in November 2004 in the upper left mammary region and another in October 2005 in the lower mammary region. She also reported 3 nodules present on the scalp since 2002 for which she had not consulted earlier.

Relevant history included the diagnosis of essential thrombocytosis in 1984 with subsequent transformation to idiopathic myelofibrosis in 1993. The patient remained asymptomatic until 1998, when she developed progressive splenomegaly, requiring therapeutic splenectomy in 2001 and the initiation of hydroxyurea therapy, followed by anagrelide. Both drugs had been discontinued due to adverse effects, although the patient continued with symptomatic treatment with regular follow-up. Due to disease progression, a bone marrow biopsy was performed in February 2004 and showed conversion of idiopathic myelofibrosis to acute myeloid leukemia. As a result, treatment with 6-mercaptopurine was initiated.

The examination revealed 2 indurated erythematous-violaceous nodules of 15 × 15 mm (upper nodule) and 10 × 8 mm (lower nodule) in the left mammary region (Figure 1). Three additional nodules of similar characteristics (10 mm, 20 mm, and 30 mm) were also observed on the scalp (Figure 2).

Histologic study of a biopsy taken from a breast lesion and another from the scalp showed a dense infiltrate in the reticular dermis composed of myeloid cells (at different stages of maturation) and megakaryocytes. Immunohistochemistry was positive for myeloperoxidase and CD68, with an insignificant number of CD34+ cells. These findings were consistent with our finding of cutaneous extramedullary hematopoiesis (Figures 3, 4, and 5).

A recent laboratory workup showed hemoglobin 90 g/L, platelets 165 × 10^9/L, and leukocytes 8.48 × 10^9/L (5% blasts, 57% neutrophils, 16% lymphocytes, 1% eosinophils and basophils, 12% leukoblasts, 2% myelocytes, and 2% metamyelocytes).

Due to slow progression of the lesions and the lack of other symptoms, a wait-and-see approach was taken. The lesions had remained stable at the time of writing.

Discussion

Idiopathic myelofibrosis is characterized by the proliferation of endothelial cells and fibroblasts in the bone marrow, resulting in disruption of the barrier between the bone marrow and peripheral blood, with subsequent migration and proliferation of hematopoietic stem cells in other organs. Extramedullary hematopoiesis in the context of idiopathic myelofibrosis was first described by Hickling in 1937 and...
In most reported cases, the foci of extramedullary hematopoiesis are the spleen and liver. Other sites include the lymph nodes, retroperitoneum, spine, kidneys, adrenal glands, gastrointestinal tract, lung, and breasts. Skin involvement is rare, and other organs such as the testicles are not usually affected. The fact that some organs are affected more often than others may result from the predilection of hematopoietic stem cells for implanting into organs already predisposed to hematopoiesis, such as the spleen or liver. A recent review of 510 patients with extramedullary hematopoiesis found that the hematopoietic foci were nonhepatosplenic in only 27 of these patients and that 18 of the 27 cases were secondary to underlying chronic idiopathic myelofibrosis.

Skin involvement is uncommon and has an estimated prevalence of 0.4% of cases. Splenectomy is believed to act as a predisposing factor for seeding of extramedullary foci of hematopoiesis in the skin through contamination during the surgical procedure or expansion of these hematopoiesis foci from the spleen to other organs, such as the liver or skin. The relationship between splenectomy and hematopoiesis in the skin is still under debate; although several cases have been described, most had no history of prior splenectomy or an excessively long time between splenectomy and onset of hematopoiesis in the skin. The cutaneous lesions can manifest in a variety of ways: as macules, papules, nodules, and even ulcers. Several cases have been described of angioma-like cutaneous lesions and others with blisters and bleeding. The most common site is the thorax and abdomen in adults and the head and neck in children. In most cases, there are usually more than 10 lesions, although isolated cases of more than 50 lesions have been reported. The diameter is usually between 0.5 cm and 5 cm, but may be larger than 10 cm. No relationship has been found between the degree of fibrosis in bone marrow and the extent of cutaneous extramedullary hematopoiesis lesions.

In most cases, the lesions tend to appear within a year after diagnosis of myelofibrosis, although an occasional case has been published of skin lesions appearing up to 8 years later or in which onset of the disease coincided with the appearance of cutaneous lesions. Histologically, the lesions are characterized by a polymorphous dermal infiltrate, composed of a combination of myeloid, erythroid, and megakaryocyte precursors. A review of case reports from patients with cutaneous extramedullary hematopoiesis by Mizoguchi et al found that a high number of cases had precursors of only 1 or 2 hematopoietic series. In children, erythroid precursors are usually predominant and megakaryocytes tend to be absent, whereas in adults, megakaryocytes are usually predominant and only half the cases with cutaneous extramedullary hematopoiesis in adults show erythroid precursors in the biopsy. Positive reactions have been observed for myeloperoxidase (myeloid series) and von Willebrand factor (megakaryocytic series) in immunohistochemical studies. Most myeloid precursor cells were only positive for myeloperoxidase, confirming their granulocytic origin. Only a few cells were positive for CD68, which is expressed in both mature and immature granulocytes and in monocytes and macrophages. In a case study published by Kwon et al, a high number of eosinophil precursors were observed; however, the significance of this is not yet clear.

The main differential diagnosis should be performed with leukemia cutis because idiopathic chronic myelofibrosis has progressed to acute myeloid leukemia in 8% of cases. In the case we describe, established acute myeloid leukemia was present when the biopsies were taken. The cutaneous infiltrate may actually not be leukemic infiltration. The long history of the lesions and the histologic characteristics of the infiltrate do not support this diagnosis, as a leukemic
infiltrate would be expected to show greater monomorphism and cell density, as well as a higher number of CD34+ cells.

Death caused by leukemic transformation of the disease has been reported, particularly when atypical megakaryocytes are present. Treatment of cutaneous extramedullary hematopoiesis is recommended if the cutaneous lesions are symptomatic or if necessary because of the site or extent, or if the underlying disease requires systemic treatment. In some published reports, the cutaneous lesions responded to treatment of the underlying disease with hydroxyurea or interferon alfa, although therapeutic failures have also occurred in both approaches. Several published case studies have described cutaneous lesions treated by electron beam with good response.

Noteworthy in the case we have described is the appearance of foci of cutaneous extramedullary hematopoiesis 9 years after the diagnosis of idiopathic myelofibrosis and the development of new foci after leukemic transformation of the disease.

Conflicts of Interest
The authors declare no conflicts of interest.

References