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Case report

Acquired ichthyosis associated with chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation in a patient with chronic myelogenous leukemia

I Dilek[1], T Demirer[1], C Ustun[1], M Arat[1], H Koç[1], M Beksaç[1], H Erdi[2], R Anadolu[2], M Ozcan[1], O Ilhan[1] and H Akan[1]

Bone Marrow Transplantation Unit, [1]Department of Hematology-Oncology, [2]Department of Dermatology Ankara University, Medical School, Ibn-i Sina Hospital, Ankara, Turkey

Summary:

Acquired ichthyosis (AI) has rarely been described following bone marrow transplantation (BMT). We report a 29-year-old male, who underwent allogeneic peripheral blood stem cell transplantation (alloPBSCT) for chronic myelogenous leukemia, and who developed AI associated with chronic graft-versus-host disease (cGVHD). Both of these disorders were treated successfully with cyclosporin A. We conclude that AI may be related to an autoimmune process on the basis of cGVHD, and dermathopathologic evaluation must be performed in patients with skin changes suggesting AI following allogeneic bone marrow transplantation.

Keywords: acquired ichthyosis; chronic graft-versus-host disease; allogeneic peripheral blood stem cell transplantation

In contrast to the inherited forms of ichthyosis, acquired ichthyosis (AI) usually begins in adult life.[1,2] AI has been described in association with a variety of conditions, including malignant diseases, renal insufficiency, malnutrition, endocrine disorders, drugs (cholesterol lowering agents), infectious diseases, autoimmune disorders,[2–4] and rarely following allogeneic bone marrow transplantation.[2] In most cases, clinical features of AI are similar to those seen in the inherited forms of ichthyosis. The histological features of AI are not specific, but in some cases resemble inherited forms of ichthyosis vulgaris.[2,5,6] Based on the literature, AI following bone marrow transplantation is very rare.[2,7] In this report, we describe a 29-year-old male patient with the clinical and histologic findings of AI following allogeneic peripheral blood stem cell transplantation (PBSCT) for chronic myelogenous leukemia (CML) who did not have a previous personal or family history of any form of ichthyosis.

Correspondence: Dr T Demirer, Dept of Hematology/Oncology and Bone Marrow Transplant Unit, Ankara University Medical School, Ibn-i Sina Hospital, Ankara, Turkey
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Case report

A 29-year-old male was diagnosed with CML in May 1995. The patient was transplanted with unmanipulated peripheral blood stem cells (PBSCs) from an HLA compatible sibling donor in first chronic phase. Conditioning was with busulphan and cyclophosphamide. PBSCs were collected from a healthy sibling following G-CSF 10 μg/kg subcutaneously, and 5×10^6 $CD34^+$ cells/kg were obtained over 2 days. GVHD prophylaxis was with 'short' methotrexate and regular schedule cyclosporin A (CsA).[7] The post-transplant days to a platelet count of $>20 \times 10^9$/l and neutrophil count of $>0.5 \times 10^9$/l were +13 and +14, respectively. There was mild skin GVHD in the first 45 days following transplantation which was well controlled with CsA. During the first 150 days post transplant the patient was seen in our medical center on routine monthly follow-up and complained of skin rashes and dryness. Cutaneous lesions of the extremities associated with large, adherent, fish scale-like squamous hyperpigmentation and hyperkeratosis were clinically characteristic of ichthyosis vulgaris (Figure 1). The patient reported that he had stopped CsA for 24 days based on his own decision because of nausea and vomiting and decreased appetite. His CsA level was 0 ng/ml



Figure 1 Brownish, large adherent fish scale-like squamas were distributed on the buttocks, and extensor surfaces of the extremities. Flexor areas such as the antecubital fossae were spared.

(therapeutic level 200–400 ng/ml). HIV test was negative and there was no evidence of any endocrinologic abnormality. He did not have a previous personal or family history of any form of ichthyosis.

Dermatopathology

Dermatopathologic examination of hematoxylin–eosin sections showed orthokeratotic hyperkeratosis, follicular plugging, thinned and a focally diminished granular layer. Increased amounts of melanin were present throughout the epidermis. There was prominent vacuolar alteration and necrotic keratinocytes in the basal layer associated with pigment incontinence and subtle evidence of satellite cell necrosis within the epidermis. A superficial mononuclear inflammatory infiltrate was also present (Figure 2). These findings were consistent with acquired ichthyosis superimposed upon early stage chronic GVHD.

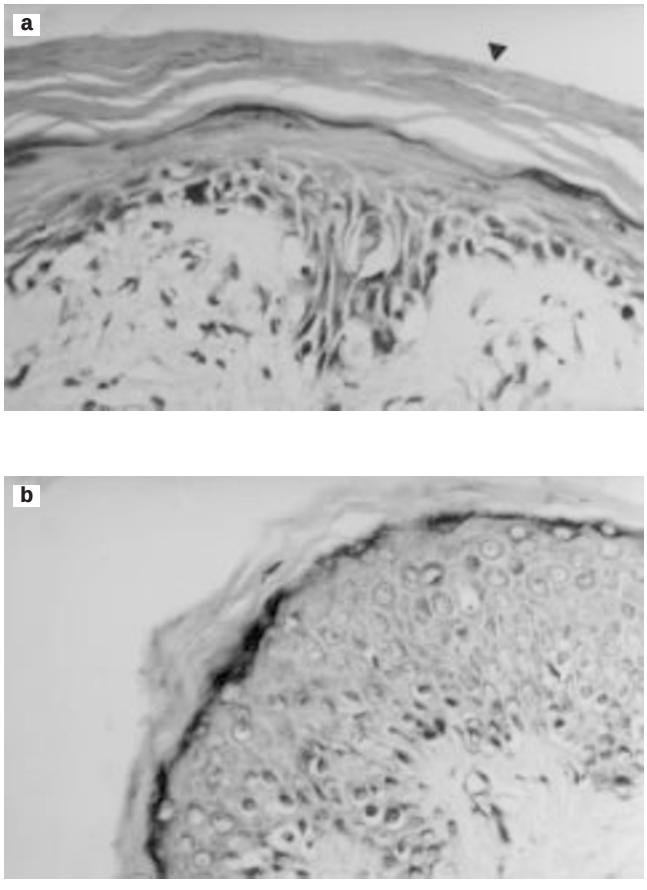


Figure 2 (**a**) Orthokeratotic hyperkeratosis, focally diminished granular layer (arrowhead), vacuolar alteration and necrotic keratinocytes were prominent. Some necrotic keratinocytes were associated with a lymphocyte infiltration known as satellite cell necrosis. (**b**) Biopsy specimen taken from the non-ichthyotic areas showed a normal granular layer (H–E × 200).

Discussion

We report a case of AI, most likely occurring as a part of the chronic GVHD process following allogeneic matched sibling PBSCT. On physical examination skin lesions on the extremities, especially the extensor aspects of the legs and arms, showed hyperpigmentation and browny desquamation which was suggestive of ichthyosis vulgaris (Figure 1). Scaly, dry skin is a common complication of BMT and GVHD but is not of the clinical pattern observed in our patient. Skin biopsies taken from the trunk showed an increased lymphocyte accumulation in the dermis which was consistent with cGVHD but biopsies from the extremities showed a thickened stratum corneum associated with hyperkeratosis, suggestive of AI (Figure 2).

It is well known that some patients with cGVHD may present with autoimmune diseases. Sometimes a scleroderma-like picture may be very prominent and disabling. Some studies have suggested that ichthyosis vulgaris may be an autoimmune disease.[2,6] Velthius *et al*[8] reported a 51-year-old man with a life long history of autosomal dominant ichthyosis vulgaris. That patient underwent renal transplantation with CsA and steroid immunosuppression and within 6 weeks after receiving a transplant, increased mobility and decreased scaling of the skin was noted. Six months later the skin was almost normal. In the current report, our patient was noncompliant with CsA and the drug was not detected in the blood. Therefore, CsA was immediately reinitiated and within 7–10 days the ichthyotic skin lesions subsided dramatically and disappeared over 3 weeks.[9] Remarkably, dermathopathologic examination of the involved skin revealed features of both AI and early stage cGVHD on the same slide, which has not been reported before. Therefore, we concluded that in this case AI may have been a part of an autoimmune disease associated with cGVHD and noncompliance with medication in a patient without a personal or family history of ichthyosis pretransplant. Although AI may be caused by some medications such as nicotinic acid, triparanol, butyrophenones, dixyrazine, cimetidine, antilipemic drugs, isotretinoin and clofazamine, our patient had not taken any of these medications.[3,5,6]

Although this ichthyosis-like disorder has been described with several diseases,[2,5,6] there were no clinical or laboratory findings of any secondary causes of ichthyosis in our case. To date, we are aware of only one report from Spelman *et al*[2] regarding AI following BMT. In that study, the authors described four cases of AI, which clinically and histologically most closely resembled ichthyosis vulgaris. In those four cases, the distribution and description of skin lesions were similar to ours. Patients had received a variety of bone marrow grafts (allogeneic mismatched, allogeneic matched, autologous), and AI did not appear to be a complication of any particular form of BMT. The authors concluded that AI may have been related to GVHD.[2]

We consider that the incidence of AI related to GVHD following allogeneic PBSCT or BMT may be more frequent than acknowledged. Therefore, skin biopsies and immunohistochemical studies should be performed in relevant cases. Considering the skin changes which were not those typically seen in cutaneous GVHD and the rapid

response to CsA we concluded that AI in this case was most likely related to an autoimmune process based upon the cGVHD.

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