CASE REPORT

Leukemia cutis originating in the extravasation site of i.v. gabexate mesilate infusion

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ABSTRACT

Leukemia cutis is a localized or disseminated skin infiltration by leukemic cells. A 64-year-old man was diagnosed with acute myeloid leukemia (AML) complicated by disseminated intravascular coagulation. During the course of treatment with gabexate mesilate, the substance accidentally leaked from the infusion site in his elbow. One month later, a dark red erythema and induration accompanied by severe pain appeared in the area proximal to the gabexate mesilate injection site. The biopsy specimen demonstrated not only inflammation but infiltration of leukemic cells as well. Immunohistochemical staining for intercellular adhesion molecule-1 and platelet/endothelial cell adhesion molecule-1 showed strong expression of endothelial cells and leukemic cells. We speculate that the gabexate mesilate might have played a role in the induction of leukemia cutis via adhesion molecules in our case. 

Key words: disseminated intravascular coagulation (DIC), extravasation, gabexate mesilate, leukemia cutis, skin complication.

INTRODUCTION

Leukemia cutis, consisting of localized or disseminated leukemic cells in the skin, presents in a variety of patterns, and may have features that overlap with those of other eruptions. The most common specific manifestations are small papules, nodules, and erythematous plaques.

Gabexate mesilate is a synthetic protease inhibitor, which is useful for the treatment of disseminated intravascular coagulation (DIC). We describe herein an unusual case of leukemia cutis which developed where an i.v. drip infusion of gabexate mesilate had leaked onto the skin.

CASE REPORT

A 64-year-old man was referred to our hospital with palpitations and general fatigue which had persisted for a month. The laboratory findings were as follows: white blood cells (WBC) 3.3 × 10^3/μL (blast cells 64%, lymphocytes 26%, neutrophils 10%, eosinophils 0%, basophils 0%, monocytes 0%), red blood cells (RBC) 153 × 10^6/μL, hemoglobin 5.0 g/dL, platelets 2.9 × 10^5/μL, aspartate aminotransferase 11 IU/L (normal, 8–38 IU/L), alanine aminotransferase 4 IU/L (normal, 4–44 IU/L) and lactate dehydrogenase 400 IU/L (normal, 106–211 IU/L). Renal functions were within normal limits, and C-reactive protein was 6.0 mg/dL (normal, <0.3 mg/dL). The results of the bone marrow aspiration showed hypercellularity and proliferation of blast cells with nuclear atypism. After the diagnosis of acute myeloid leukemia (AML-M2) was made, he was treated with systemic chemotherapy using melphalan (2 mg/every other day). After 2 weeks of medication, the laboratory data showed improvement. Specifically, WBC was 2.9 × 10^3/μL with the blast cell count at 18%. However, the patient suffered from DIC due to bacterial pneumonia, and was subsequently treated with gabexate mesilate, which accidentally leaked from the infusion site in his elbow. On the following day,
he visited our department for the treatment of induration and pain in the affected area, which were improved by means of topical steroid ointment.

One month later, he consulted us again following the appearance of a dark red erythema and induration accompanied by severe pain in the area proximal to the gabexate mesilate injection site. At first he was thought to be suffering from delayed cutaneous damage caused by the extravasation of gabexate mesilate, and was given topical applications of steroid ointment and s.c. steroid injections once daily for several days. During the course of the steroid therapy, several firm, bean-sized, dark-red nodules appeared on his left forearm. Closer physical examination revealed a few bean-sized, reddish nodules near the antecubital fossa (Fig. 1). The top of the nodules had necrotized and become ulcerated. A biopsy specimen from the nodules showed slight lymphocyte exocytosis into the epidermis, and massive infiltration of lymphocytes, histiocytes and neutrophils with nuclear dust from the superficial dermis to the subcutis (Fig. 2a). Extravasation of RBC was prominent and fibrinoid degeneration of vessels and collagen fibers was observed. Granulation tissue and granulomata were observed throughout the dermis. Atypical cells compatible with acute myeloid leukemic cells were observed in the dermis (Fig. 2b). Most of

Figure 1. Firm, bean-sized nodules in region proximal to the gabexate mesilate injection site.

Figure 2. (a) Dense infiltration of lymphocytes and histiocytes in all layers of the dermis. (b) Atypical cells with large nuclei were infiltrated mostly in the mid-dermis. Bleeding and fibrinoid degeneration of vessels were observed.
these atypical cells were positive for myeloperoxidase, indicating that the infiltrated atypical cells were leukemic (Fig. 3). Immunohistochemical staining for intercellular adhesion molecule-1 (ICAM-1) and platelet/endothelial cell adhesion molecule-1 (PECAM-1) and vascular cell adhesion molecule-1 (VCAM-1) revealed strong expression of leukemic cells and inflammatory cells. In addition, endothelial cells were positive for ICAM-1 and PECAM-1 (Fig. 4). Periodic acid-Schiff, Gram, Grocott, and Ziehl–Neelsen stains were all negative. On the basis of these findings, the patient was diagnosed with leukemia cutis originating at the site of the gabexate mesilate extravasation. The ulcerative skin lesions were treated with silver sulfadiazine cream. Although the patient received systemic chemotherapy, he died due to intracranial hemorrhaging 3 months after the appearance of the cutaneous nodules.

**DISCUSSION**

Our case was remarkable in that well-defined leukemic nodules appeared following extravasation of a drip infusion. Growth of leukemia cutis does not favor any particular site, but secondary occurrences on injured sites such as burn scars, traumata, herpes zoster eruption sites and surgical scars have been reported.1,2 To our knowledge, there are no prior cases of the occurrence of leukemia cutis or of skin metastases at the site of the extravasation of gabexate mesilate.

Gabexate mesilate is a synthetic protease inhibitor (an anti-inflammatory serine protease inhibitor) with anticoagulant properties, which is useful for the treatment of acute pancreatitis, adult respiratory distress syndrome and DIC. Because gabexate mesilate is a cytotoxic agent, when it leaks or is used in high concentrations, skin ulcers, panniculitis, swelling, indurations and erythema can occur, and are indeed reported as complications resulting from the use of this drug.3 Although the details of the mechanisms remain unclear, these complications are thought to result directly from vascular damage. Additionally, in several cases, dense eosinophilic infiltration in the extravasated site has been reported, suggesting that an allergic reaction to mesilate gabexate might be connected with the occurrence of the skin complications.4 Furthermore, it should be
noted that half of the dermatological symptoms caused by the extravasation of gabexate mesilate developed more than 1 month after the extravasation, whereas gabexate mesilate has a half-life of less than 1 min. Therefore, we initially suspected that our case was one of delayed inflammation due to the extravasation of gabexate mesilate. The biopsy, however, demonstrated not only inflammation but infiltration of leukemia cells as well.

We speculate that leukemia cutis in our case may have developed at the extravasation site for the following several reasons:

1. Leukemia cutis might have developed by chance at the site of the lesion.
2. The gabexate mesilate might have been the direct cause of the recruitment of the leukemic cells.
3. Frequent steroid injection might have attracted leukemic cells.
4. Tissue damage that resulted from the extravasation of gabexate mesilate might have resulted in inflammation and bleeding, leading to the accumulation and proliferation of leukemic cells.
5. Vascular injury due to extravasation of gabexate mesilate might have triggered the subsequent events through cell adhesion molecules and chemokines, and induced accumulation of leukemic cells.

Specifically, the endothelial cells are activated in an inflammatory response, and leukocytes are then mobilized by a complex response from the activated endothelial cells. This includes the clustering of adhesion molecules, such as ICAM-1, PECAM-1, VCAM-1, E-selectin, and so on. Leukocyte adhesion and formation of the docking structure is associated with the clustering of adhesion and signaling molecules. This clustering is important to perform transendothelial migration efficiently. In particular, ICAM-1 is one of the molecules most involved in the transcellular migration process. ICAM-1 expression on endothelial cells is greatly upregulated in inflammations, and some kinds of leukemic cells such as adult T-cell leukemia and hairy-cell leukemia highly express ICAM-1. Moreover, VCAM-1 is preferentially expressed by leukemia (acute lymphoblastic leukemia) cells and absent from normal bone marrow precursor cells. It is known that PECAM-1 is expressed on the surface of leukemic cells in many patients with B-cell chronic lymphocytic leukemia. In our case, the leukemic cells expressed ICAM-1, PECAM-1 and VCAM-1. We speculate that the inflammation caused by the gabexate mesilate may have affected the adhesion molecules on the endothelial cells involved in leukocyte transendothelial migration. Indeed, the findings that endothelial cells were positive for ICAM-1 and PECAM-1 in our case (Fig. 4) might be seen as corroborating this explanation. Gabexate mesilate might easily provoke an inflammatory response, which may in turn help trigger the leukemia cutis.

We must be aware that the extravasation of tissue-damaging drugs, such as anticancer agents and enzymatic agents, are a potential cause of malignant cell seeding and accumulation.

REFERENCES

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