

Therapy-related Leukaemia Cutis after Adjuvant Chemotherapy in a Breast Cancer Patient

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Therapy-related acute myeloid leukaemia (t-AML) is a complication following exposure to cytotoxic agents used in the treatment of various primary malignancies (1). Similar to *de novo* AML, t-AML is a clonal haematopoietic disorder frequently associated with chromosomal and molecular changes. However, the prognosis and long-term survival rates of t-AML are significantly worse. Due to the increasing use of chemotherapy, and improved survival rates with cancer treatment, there has been an increasing incidence of t-AML. Rarely, leukaemia cutis can be the initial presentation of t-AML.

CASE REPORT

A 56-year-old Chinese woman was initially diagnosed with an infiltrating ductal carcinoma of the left breast with no evidence of metastasis. A simple mastectomy of the left breast with axillary clearance was performed and she was subsequently treated with adjuvant chemotherapy of cyclophosphamide and doxorubicin for 4 cycles with complete remission. Eighteen months later, she presented with an asymptomatic rash for 3 weeks. Clinical examination revealed extensive erythematous, firm papules distributed over her trunk, neck and limbs (Fig. 1). There was no mucosal involvement, lymphadenopathy or organomegaly. Her initial complete blood count were as follows: haemoglobin 10 g/dl (normal 12.0–16.0), white blood cells $9.9 \times 10^9/l$ (normal 4.0–10.0), differential count: neutrophils 36.4%, lymphocytes 25.3%, monocytes 37.3%, eosinophils 0.1%, platelets $224 \times 10^9/l$ (normal 140–440).

A skin biopsy was performed from her trunk, which showed a grenz zone with multifocal perivascular infiltrate of immature mononuclear cells throughout the dermis (Figs 2A and B). Immunohistochemical studies revealed that neoplastic cells were positive for myeloperoxidase (MPO), CD68, (Figs 2C and D) and CD43. The neoplastic cells were negative for CD3, CD1a, S100, LCA, CD20, CD34 and CD117. Morphological and immunophenotypical findings were consistent with AML with monocytic differentiation (AMMoL/AMoL, World Health Organization (WHO) classification).

Bone marrow smears showed hypercellularity with increased blasts. The neoplastic cells were positive for MPO, Sudan black B, and alpha naphthyl butyrate on immunohistochemical studies. These features were consistent with acute monocytic leukaemia (AMoL) subtype. A bone marrow trephine biopsy confirmed morphologically the involvement of AML with features of monocytic differentiation. Flow cytometry analysis of bone marrow showed 73% of blasts, which were positive for CD13, CD33, CD11b and MPO, and negative for CD117 and CD64. Cytogenetic analysis showed a reciprocal translocation between chromosome 6 and 11, with a breakpoint at band q23.

The patient was treated with a combination chemotherapy of idarubicin and cytarabine arabinoside and received consolidation with high-dose cytarabine arabinoside. A bone marrow transplant was performed, which was complicated by graft rejection and neutropaenic sepsis. The patient died 11 months after the initial diagnosis.

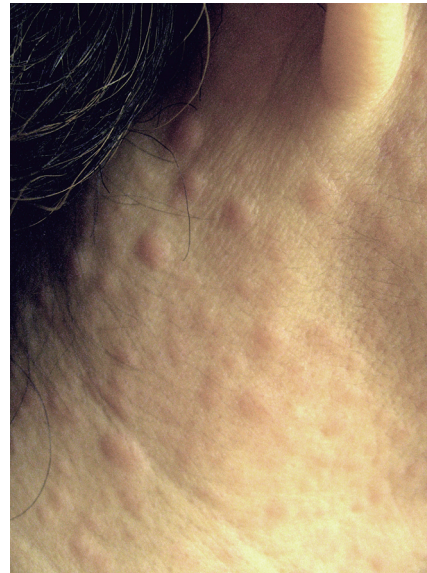


Fig. 1. Erythematous papules on the neck.

DISCUSSION

The risk of developing AML 10 years after any adjuvant chemotherapy for breast cancer in older woman is low (1.8%) but increasing (2). The latency between the treatment of the initial malignancy and the secondary AML ranges between several months to years and is dependent on the specific cytotoxic used, the cumulative dose and intensity.

Adjuvant chemotherapy for breast cancer received in our patient included the use of both topoisomerase II inhibitors (doxorubicin) as well as alkylating agents (cyclophosphamide). Both agents are known to induce t-AML, but with unique differences (3). Alkylating agent-associated t-AMLs have a long latency period, with onset usually occurring 4–6 years after treatment. They may also present with a myelodysplastic or preleukaemic phase. The leukaemias are commonly of the AML subtype and are associated with chromosomes 5 and 7 abnormalities. Leukaemias induced by topoisomerase II inhibitors, on the other hand, have a shorter latent period of 12–36 months (4), lack a preleukaemic phase, are associated with 11q23 abnormalities and usually present with acute myelomonocytic leukaemia (AMMoL) or AMoL subtypes. The latter findings were dominant in our case.

The aetiological and predisposing factors for t-AML are unclear. However, increased risks have been attributed to defects in both DNA repair, as well as genetic polymorphisms in detoxification genes (5). In topoisomerase

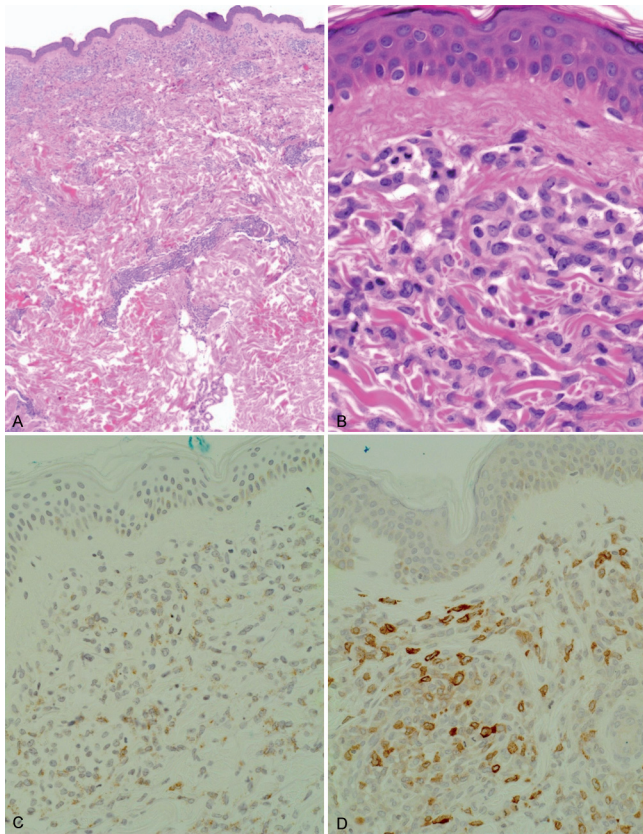


Fig. 2. (A) Grenz zone with multifocal perivascular infiltrate (haematoxylin and eosin (H&E) $\times 20$). (B) Immature mononuclear cells distributed through the dermis (H&E $\times 200$). (C) Positive immunostaining for myeloperoxidase. (D) Positive immunostaining for CD 68.

inhibitors-associated t-AML, balanced chromosomal translocation involving the MLL gene at 11q23 (6, 7).

The median survival of t-AML is 6.9 months and is considered to have shorter survivals than *de novo* AML. Allogeneic bone marrow transplantation (BMT) is the treatment most likely to cure t-AML. However, even with transplant, the estimated 2-year survival rate is 30% and relapse rate is 42% (8). Our case also received BMT, but the result was not successful.

Cutaneous infiltration of AML occasionally precedes the involvement of the bone marrow or peripheral blood and is called as "leukaemia cutis". Leukaemia cutis of t-AML has rarely been reported. The various manifestations of leukaemia cutis include solitary or multiple reddish to violaceous papules, plaques and nodules or generalized erythematous maculopapular eruption (9). Histologically, CD68, lysozyme and MPO are useful to detect myeloid leukaemia cutis (10). AMMoL/AMoL (WHO) more commonly involves the skin than do other types of myeloid leukaemia (11, 12). This also could be supported by the fact that few cases of leukaemia cutis of t-AML were reported following the treatment of topoisomerase inhibitors (13, 14). The mechanism of skin

infiltration is unclear (10), but it is believed to occur as a result of tissue-selective homing of a unique subpopulation of malignant myeloid clones. In AMMoL/AMoL, it has been proposed that their more mature blasts are better primed for early migration from the bone marrow and invasion of various other tissues, resulting in a higher incidence of extramedullary disease (15).

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