A cutaneous manifestation of acute lymphoblastic leukaemia mimicking urticaria pigmentosa

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Summary

A 37-year-old female developed what appeared to be the typical cutaneous manifestations of urticaria pigmentosa. These preceded the peripheral blood changes of acute null cell lymphoblastic leukaemia and skin biopsy revealed that the cutaneous changes were due to leukaemic infiltration. Chemotherapy resulted in clearance of the rash. The importance of skin biopsy in patients presenting with suspected urticaria pigmentosa is emphasized.

KEY WORDS: skin biopsy, chemotherapy, pruritus.

Case report

A 37-year-old Caucasian female presented with a 6-week history of an itchy skin rash which started on the shoulders and spread to involve the trunk and upper arms. The itching was made worse by a hot bath and firm pressure on her skin was painful. The rash was made more prominent by scratching.

Three months previously she had developed numbness of the right side of her face which resolved spontaneously. She then developed a 'flu-like' illness accompanied by shortness of breath. Investigations revealed a normal peripheral blood count, white cell differential and film but the ESR was raised at 130 mm/hr. A chest X-ray showed a diffuse pulmonary infiltrate and reduced carbon monoxide diffusion was present on respiratory function testing. Cytoid bodies were present on ophthalmological examination. Anti-nuclear and anti-ds DNA antibodies were absent and complement fractions C₃ and C₄ were normal.

A trial of steroid therapy (prednisolone 10 mg/day) resulted in improvement in well being and exercise tolerance.

During the next 6 weeks she developed the skin changes described above. There was no significant past medical history and in particular no personal or family history of similar skin disease.

Examination revealed a pale woman with a light brown pigmented macular eruption. This was present predominantly over the back and chest but extended to her upper arms (Fig. 1). Light stroking of these lesions caused marked urtication. In addition light pressure on the affected areas caused tenderness. These clinical findings were considered to be diagnostic of urticaria pigmentosa.

Left cervical and bilateral axillary lymphadenopathy was also noted. The remainder of the physical examination was normal.

She was mildly anaemic (haemoglobin 11.0 g/dl) had a low total white cell count of $3.6 \times 10^9/l$ with neutropenia of $0.43 \times 10^9/l$ and had circulating blast cells ($0.4 \times 10^9/l$). Serum immunoglobulins were normal. Before further investigations were performed the probable diagnosis was considered to be systemic mastocytosis.

A bone marrow aspirate revealed replacement by a blast cell population with features of lymphoblasts. Cytochemical examination demonstrated the blasts to be negative for peroxidase, periodic acid-Schiff, chloroacetate esterase, non-specific esterase and acid phosphatase.

Cell typing demonstrated that 70% of the blasts were positive for the lymphoblastic marker terminal deoxynucleotidyl transferase. The blasts were negative for the common ALL antigen and for T and B markers (E-rosettes and anti-Ig). These results were compatible with a diagnosis of acute lymphoblastic leukaemia of the null cell type.

A bone trephine biopsy showed extensive marrow involvement by blast cells but with no increase in mast cells.

FIG. 1. Pigmented macules on trunk which urticated on pressure.

FIG. 2. Perivascular dermal infiltrate of lymphoblasts, H.E. $\times 144$.

A skin biopsy of a non-traumatized macule (Fig. 2) showed a monomorphic population of blast cells in a perivascular distribution within the papillary and upper reticular dermis. Stains for mast cells (chloroacetate esterase, toluidine blue, aldehyde fuchsin) were negative. The basal layer of epidermis showed a marginal increase of melanin. The appearance was considered to represent infiltration of the skin by lymphoblastic leukaemia and not urticaria pigmentosa. Immunoperoxidase studies showed no localiza-

tion of immunoglobulin or complement in the biopsy.

Initially before the results of cell marker studies were known, the lymphoproliferative disorder was considered to be lymphoblastic non-Hodgkin's lymphoma. Consequently chemotherapy was commenced with cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP regimen). Additionally because of the history of facial numbness the patient also received intrathecal methotrexate. However

computerized tomographic brain scan and cerebrospinal fluid cytospin cytology showed no definite evidence of central nervous system involvement. Within 4 days of commencement of chemotherapy the cutaneous symptoms had disappeared and within 7 days the rash had cleared.

In view of the extremely favourable response to CHOP therapy, this was continued even though cell marker studies subsequently showed that the accurate diagnosis was null cell acute lymphoblastic leukaemia. A full haematological remission was obtained.

Five months later the skin rash recurred with a distribution similar to that at the time of diagnosis although scalp involvement was readily apparent due to coexistent drug-induced alopecia. The white cell count had risen to $94 \times 10^9/l$ (99% blasts). The bone marrow findings were identical to those present at diagnosis. Chemotherapy was commenced with three daily doses of adriamycin and continuous infusion cytosine arabinoside for 5 days. By day four the skin symptoms had disappeared and mechanical trauma failed to produce urtication. The rash had disappeared by day 9.

Discussion

This patient presented with the typical skin manifestations of urticaria pigmentosa. The presence of a pigmented macule or nodule which urticates when traumatized is usually considered to be diagnostic of mast cells in the underlying dermis (Rook, Wilkinson and Ebling, 1979). Hence a diagnosis of systemic mastocytosis was suspected on finding the peripheral blood change. However this was firmly excluded by skin biopsy on which special stains for mast cell markers were negative. The demonstration of blasts in the marrow that were positive for terminal deoxynucleotidyl transferase (tdt) activity indicated a diagnosis of acute lymphoblastic leukaemia. Tdt is negative in B cell non-Hodgkin's lymphoma (Janossy, Ganeshaguru and Hoffbrand, 1982) and the absence of E-rosette formation militates against a diagnosis of T cell lymphoma or leukaemia.

We consider that the lymphoblastic skin infiltrate was the cause of the clinical picture which mimicked urticaria pigmentosa. This is supported by the skin biopsy findings, initial response to chemotherapy and re-emergence of the rash at the time of relapse. In addition reinduction therapy again led to the disappearance of the rash. It is of interest to note that the rash preceded the peripheral blood changes.

Although the association of T cell lymphoma/leukaemia and skin lesions is well-established, skin involvement in acute lymphoblastic leukaemia is rare. Boggs, Wintrobe and Cartwright (1963) recorded an incidence of only 1% in an extensive

review of the literature. There is one previous report of urticaria pigmentosa associated with acute lymphoblastic leukaemia (Fromer and Jaffe, 1973) and in this case the skin manifestations were present at the age of 3 weeks preceding the diagnosis of acute lymphoblastic leukaemia by 5½ years. There was no response of the skin lesions to chemotherapy and it would seem unlikely that they were caused by a leukaemic infiltrate. The authors suggested that urticaria pigmentosa might predispose to the development of leukaemia. Various other haematological malignancies have been associated with urticaria pigmentosa and include Hodgkin's disease, lymphocytic lymphoma, acute myelomonocytic leukaemia, chronic lymphocytic leukaemia and polycythaemia rubra vera (Weidman and Franks, 1963; Cooper, Winkleman and Wiltzie, 1982; Bowdler and Tullett, 1960; Handler, Isenberg and Greaves, 1981). In all cases the diagnosis of urticaria pigmentosa was confirmed histologically and the disease remained unresponsive to chemotherapy. Our case appears to be unique in that the leukaemic cell infiltrate masqueraded as urticaria pigmentosa.

Exactly why this patient displayed this unusual skin manifestation is unclear. Pigmentation and urticaria have been associated with acute leukaemias showing basophilic differentiation both *de novo* and as terminal transformation of chronic granulocytic leukaemia (Wick, Chin-Yang Li and Pierre, 1982). Similar symptoms and signs have been noted in chronic granulocytic leukaemia with extreme basophilia (Rosenthal, Schwartz and Canellos, 1977). However these cases have also displayed other hyperhistaminaemic manifestations, such as diarrhoea, bronchospasm and oedema. Some of these cases when treated displayed further evidence of hyperhistaminaemia and it would seem unlikely that histamine was the pathogenetic mechanism in this case. Acute leukaemia cells are known to be capable of producing peptides such as ACTH like substances and it is tempting to speculate that in this case a vasoactive peptide was produced by the leukaemic cells and released by pressure on the skin.

This case highlights the importance of skin biopsy in confirming the clinical diagnosis of urticaria pigmentosa and in the investigation of skin rashes in leukaemic patients.

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