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# Evidence of Responsiveness to Chemotherapy in Aggressive Rosai–Dorfman Disease

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SINUS HISTIOCYTOSIS with massive lymphadenopathy (Rosai–Dorfman disease) is a rare histiocytic syndrome with well-defined histological features, characterised by nodal, or less frequently extranodal, infiltration by histiocytes, accompanied by small lymphocytes, mature plasma cells and red cells [1]. The disease is often benign, self-limiting and subject to spontaneous regression. In the last few years, a number of studies have described pathological and laboratory findings and the characteristics of approximately 800 patients have been collected in a register [2]. However, limited data have been reported on the tolerance and activity of chemotherapeutic regimens when disease manifestation becomes severe and progressive, and no long-term follow-up information is available for the patients [3].

In 1979, a 48-year-old man with a previous history of myocardial infarction presented with nodular cutaneous and subcutaneous lesions and axillary plus supraclavicular lymph nodes that had progressed in the previous 6 months. Histological examination of one subcutaneous nodule and one supraclavicular lymph node revealed at low power examination a thickened lymph node capsule and a parenchyma with markedly dilated sinuses filled with bland-appearing histiocytic cells (Figure 1A). At higher magnification, these cells had abundant amphophilic to eosinophilic cytoplasm, and occasionally showed lympho- and erythrophagocytosis (Figure 1B). Nuclei appeared round to oval, normochromic with slight indentations of the nuclear membrane. A diagnosis of Rosai–Dorfman disease was made and confirmed by external review.

A staging examination revealed mild normochromic normocytic anaemia, leucocytosis, hypergammaglobulinaemia and altered baseline cupraemia and carcinoembryonic antigen (CEA) values. A gallium scan found diffuse disease deposits on the chest, abdomen and arms, and a bone scan confirmed the presence of multiple bone lesions. Bone X-rays defined multiple sites of bone lysis. Radiation therapy (40 Gy) was given in July 1979 to a lytic lesion judged at risk of fracture. Owing to the presence of increasing bone pain and growing nodules, the patient was treated from August 1979 with cyclophosphamide (600 mg/m$^2$ days 1, 8), vincristine (1.2 mg/m$^2$ day 1) and methylprednisolone (40 mg days 1, 8), with cycles repeated every 28 days. After 12 cycles, a partial response was assessed through bone and gallium scan and objective examination. A significant decrease in bone pain was obtained. Therapy was discontinued after 16 cycles with no significant side-effects

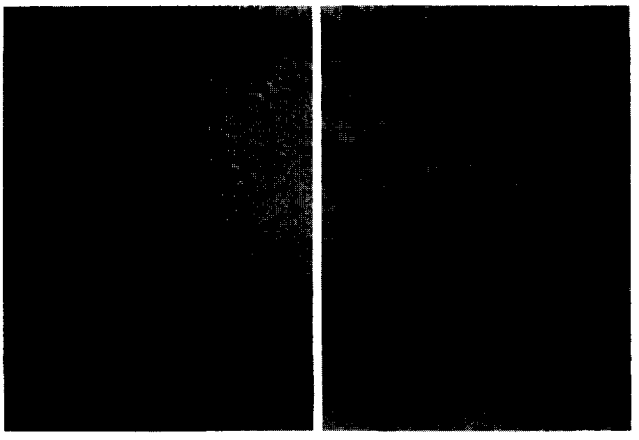

**Figure 1. Sinus histiocytosis with massive lymphadenopathy. (A) A predominantly diffuse pattern of lymph node involvement is observed at low magnification (H&E, x40). (B) Characteristic cells with abundant cytoplasm (H&E, x250).**

recorded. Two years later, new bone lesions were observed on a follow-up bone scan, and the patient received five more cycles of therapy with a new partial response. One year later, new progression of disease was observed in lymph nodes and cutaneous nodules, and another five cycles of therapy were delivered with remission of disease. Once again in 1985, new subcutaneous nodules were noted and nine cycles of the same therapy were delivered with partial tumour remission. The remission lasted until 1991, when, due to the presence of superficial nodes, new bone lesions and cutaneous nodules, a new regimen comprising oral etoposide (100 mg days 1–3) and prednisone (50 mg, days 1–5) was delivered. After three cycles of therapy and partial remission of disease, the patient died as a result of a myocardial infarction after a follow-up of 12 years.

To date, no systematic treatment study of sinus histiocytosis with massive lymphadenopathy has been performed [3, 5]. Most case reports have focused on pathological features and failed to provide clear information useful for treatment evaluation such as pre- and post-treatment objective measurement of disease sites [4–6]. Our case demonstrated a clear responsiveness to chemotherapy and a disease evolution mimicking a low-grade non-Hodgkin's lymphoma. The results achieved in this patient suggest that symptomatic progressive Rosai–Dorfman disease may require an approach similar to that commonly employed with low grade lymphomas. Long-lasting remissions can be achieved with alkylating or epipodophyllotoxin-containing regimens, with a related long survival. However, a series of uniformly treated patients is required to clarify the role of chemotherapy in Rosai–Dorfman disease.

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