

## Histiocytic medullary reticulosis occurring with small cell lung carcinoma

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**ABSTRACT:** Haematophagocytic activity is a salient feature of malignant histiocytic medullary reticulosis. This potency has also been observed as an aberrant property of non-histiocytic malignant cells or as a benign histiocytic process in response to infections or malignancies. We report the case of a patient who presented simultaneously with a limited stage small cell lung carcinoma and a fatal reactive form of histiocytosis. We conclude that such a haematophagocytic syndrome may occur in the setting of small cell lung carcinoma as previously described in other malignancies.

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Histiocytic medullary reticulosis (HMR) is pathologically characterized by widespread tissue infiltration by atypical histiocytes demonstrating haematophagocytosis [1, 2]. Recently an increasing number of HMR has been reported in association with various malignancies mostly of lymphoid [3-11] or haematopoietic lineage [12-14]. Such a haematophagocytic syndrome may include two distinct entities: malignant histiocytosis and a benign (but potentially fatal) reactive histiocytic process mimicking the malignant form. We report the first case of a patient who presented simultaneously with a limited stage small cell lung carcinoma (SCLC) and an HMR.

### Case report

A 75 yr old patient was admitted to hospital in April 1987 because of loose cough and persistent chest X-ray changes. He was a life-long smoker. His past medical history was limited to mild pancytopenia discovered six months previously and investigated in another hospital. The patient felt well without persistent fever or weight loss. Physical examination was negative. Chest X-ray showed an opacity in the apical segment of the right lower lobe. Fibreoptic bronchoscopy disclosed an irregular stenosis of the apical segmental bronchus of the right lower lobe. Biopsies revealed pure oat cell carcinoma. Immunohistochemical staining was positive with anti-neurone specific enolase and anti-cytokeratin antibody. Brain and abdominal computed tomography disclosed no evidence of metastases. Pertinent laboratory studies included serum sodium  $126 \text{ mmol}\cdot\text{l}^{-1}$  with

hypouricaemia  $165 \text{ mmol}\cdot\text{l}^{-1}$ , calculated serum osmolality was  $263 \text{ mOsm}\cdot\text{kg}^{-1}$  and urinary osmolality  $467 \text{ mOsm}\cdot\text{kg}^{-1}$ . Bilirubin, lactate dehydrogenase and alkaline phosphatase were within normal range. Blood examination revealed a haemoglobin level of  $9.2 \text{ g}\cdot\text{dl}^{-1}$  and a white blood cell count of  $900\cdot\text{mm}^{-3}$  with 40% neutrophils and a platelet count of  $130,000\cdot\text{mm}^{-3}$ . Bone marrow biopsy and aspirate disclosed a hypocellular marrow with foci of cells with an abundant vacuolated cytoplasm containing phagocytosed cellular debris suggesting tremendous phagocytosis of blood cells (mostly erythrocytes). Most cells had a mature appearance. Immunohistochemical staining was negative with anti-neurone specific enolase or cytokeratin. Non-specific esterase were positive. Electron microscopic examination confirmed haematophagocytosis by histiocytic-like cells (fig. 1). Anti-human immunodeficiency virus (HIV) antibody were negative by enzyme-linked immunoadsorbent assay (ELISA). Serological studies for Epstein Barr virus and cytomegalovirus were negative. On the basis of these findings the diagnosis of limited SCLC with HMR possibly in a reactive form was made.

Chemotherapy was initiated in May with cisplatin  $35 \text{ mg}\cdot\text{m}^{-2}$  and etoposide  $75 \text{ mg}\cdot\text{m}^{-2}$ , both given daily for 3 days. Three weeks later the chest X-ray and the serum sodium became normal; however, the patient's haematological status deteriorated. Despite supportive therapy, he died in July of a bronchopneumonia. The autopsy revealed invasive pulmonary aspergillosis and no macroscopic or microscopic evidence of SCLC. In addition, the spleen was enlarged (290 g). Mature erythrophagocytic histiocytes were observed in the

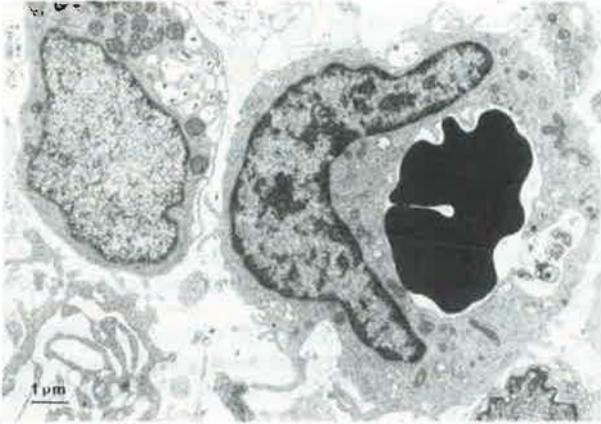


Fig. 1. — Electron microscopy of bone marrow demonstrating histiocytic-like cells containing phagocytosed erythrocyte (uranyl acetate and lead citrate).

splenic red pulp, the hepatic sinusoids and the bone marrow. No pathological evidence of viral infection could be observed.

### Discussion

This case illustrates the simultaneous occurrence of a limited stage SCLC and of an HMR involving bone marrow, spleen and liver. Pathological review of all available tissue was consistent with a reactive form of HMR and demonstrated that the malignant bronchial and the medullary haematophagocytic cells bear different phenotypical features. The syndrome of inappropriate antidiuretic hormone secretion was reasonably related to SCLC. Indeed, this syndrome is the most frequent paraneoplastic manifestation associated with SCLC [15] and has not been described in HMR, except in very few malignant diseases with lung involvement [2]. After chemotherapy, divergent courses were observed: the SCLC apparently vanished but the HMR progressed. Death was related to invasive pulmonary aspergillosis, an opportunistic infection mainly observed in the setting of prolonged granulocytopenia [16]. To our knowledge, this is the first report of a HMR associated with a SCLC. However, Spivac [17] described one patient with a SCLC associated with an intra-medullary haematophagocytosis but the phagocytic cells were described as metastatic epithelial cells and not as histiocytes.

The simultaneous occurrence of these two aggressive disorders is unlikely to be coincidental and raises questions about their relationship. Most of the previously described malignant conditions associated with haematophagocytic syndrome were of lymphoid [3–11] or haematopoietic [12–14] lineage but in few cases mediastinal germ cell tumour [18, 19] and carcinoma of various origins have also been reported [17, 19–22]. Different mechanisms may be involved in the pathogenesis of such associations.

Firstly, the tumour cells unrelated to monocyte macrophage system (MMS) may have acquired phagocytic ability. After bone marrow invasion these cells could mimic a HMR. Such a mechanism has been described in cases of T-cell lymphoma [9] and in breast or lung carcinoma [17, 21].

Secondly, malignant histiocytic cells and the associated neoplasm may originate from a common stem cell in spite of different phenotypes. This hypothesis has been advocated in cases of lymphoid or haematopoietic neoplasm, so true is it that such malignancies are prone to change in their appearance [23]. That SCLC may originate from the MMS has been suggested by the existence of common antigens in the SCLC cells and in the macrophages [24]. However, there are several lines of evidence that bronchial carcinoma, whatever its pathological appearance, originates from a common malignantly transformed bronchial stem cell [15]. Thus, the hypothesis that SCLC and HMR may originate from the same stem cell seems unlikely.

Finally, the reactive form of HMR following infection with bacteria, fungi, parasites and viruses is now well recognized [25]. An underlying immunodeficiency state seems to be a usual prerequisite condition, often related to haematological malignancy and/or chemotherapy. An acute onset with fever and pancytopenia is usual. Infection by cytomegalovirus, Epstein-Barr and other opportunistic viruses are often demonstrated. Despite an unpredictable prognosis, a favourable outcome is frequent, highlighting the non-malignant nature of this process. Phagocytosis is more prominent and cells are of more mature appearance in infection-associated HMR than in malignant histiocytosis [25]. The cancer-associated haematophagocytic syndrome is another type of reactive HMR described in conjunction with various malignancies including T and B lymphoma [10], Hodgkin's disease [11], gastric carcinoma [20] and mediastinal germ cell tumour [18, 19]. The mechanism of the MMS activation is unclear. Cytokines released by lymphomatous T-cells [10], secretion of tumour growth factors for MMS [18], and MMS stimulation by tumour antigens [11, 18] are possible explanations. In the present case the insidious onset of the HMR, the absence of immunosuppression and the negative laboratory data do not support an infectious origin.

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*Histiocytose médullaire associée à un carcinome bronchique à petites cellules. H. de Cremoux, I. Monnet, J. Fleury, C. Chleq.*

RÉSUMÉ: L'érythrophagocytose est exceptionnellement le fait de cellules malignes de lignée non histiocytaires. Plus souvent elle est le fait d'histiocytes malins ou simplement activés par un processus infectieux ou tumoral. Nous rapportons l'observation d'un patient qui avait simultanément un cancer bronchique à petites cellules localisé au thorax et une forme réactive d'histiocytose d'évolution fatale. Cette forme d'érythrophagocytose peut donc survenir en cas de cancer bronchique à petites cellules ainsi que cela a déjà été décrit lors d'autres affections malignes. *Eur Respir J.*, 1991, 4, 122–124.