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Pulmonary Langerhans' cell histiocytosis (histiocytosis X) following metastasising malignant melanoma

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Summary

Background: Pulmonary Langerhans' cell histiocytosis (histiocytosis X) is an uncommon, diffuse interstitial lung disease of unknown cause, mostly presenting in young smokers. Association of pulmonary Langerhans' cell histiocytosis with a malignant neoplasm is rare.

Case description and results: We present and discuss the case of a 48-year-old man (ex-smoker) with metastasising malignant melanoma. A few months after chemotherapy and a modified Whipple procedure for retroduodenal metastasis of a malignant melanoma, computer tomographic scans revealed intrapulmonary "ring-shaped structures". Endobronchial biopsies and bronchioalveolar lavage showed no evidence of neoplasm or inflammation. Open-lung biopsy was performed and revealed pulmonary Langerhans' cell histiocytosis.

Conclusion: To our knowledge this is the first reported case of pulmonary Langerhans' cell histiocytosis in association with malignant melanoma. Chemotherapy for malignant melanoma may be related to the development of pulmonary Langerhans' cell histiocytosis.

Key words: Langerhans' cell histiocytosis; Langerhans' cell granulomatosis; histiocytosis X; open-lung biopsy; retroduodenal metastasis; chemotherapy

Introduction

Pulmonary Langerhans' cell histiocytosis, also known as histiocytosis X or Langerhans' cell granulomatosis, is an uncommon, diffuse interstitial lung disease primarily presenting in young adults. The disease is characterised by bronchiolocentric inflammation with secondary vascular changes. An association with malignancies is unusual, though occasionally documented [1]. We report a case of pulmonary Langerhans' cell histiocytosis associated with malignant melanoma, which we believe to be the first such case reported.

Case report

The patient was a 48 year old man with a medical history of metastasising malignant melanoma. The patient was an ex-smoker, reporting occasional cigarette smoking prior to the diagnosis of malignant melanoma.

Eight years previously a malignant melanoma of lentigo maligna melanoma type (1.2 mm thickness, Clark's level IV) was removed from the left proximal neck. He remained well for two years before lymphogenic metastasis occurred and left neck dissection had to be performed. Two years later local recurrence of the malignant melanoma developed and surgical resection was performed. A further two and half years later repeat local recurrence necessitated surgical resection. He remained well for one further year before lymphatic metastasis reoccurred and repeat left neck dissection had to be performed. Three months later a metastatic lymphatic node of the left neck was resected and six months later left axillary dissection had to be performed for lymphatic metastasis. Four months after axillary dissection he developed abdominal symptoms with pain, vomiting, nausea and loss of appetite. Further diagnostic evaluation showed a large retroduodenal tumour and chemotherapy was started (tamoxifen, dacarbazine, cisplatin and carmustine). At the end of the first chemotherapy cycle the abdominal symptoms increased. Endoscopy showed significant duodenal stenosis and a modified Whipple procedure was performed. Histological examination of the tumour revealed metastasis of the known malignant melanoma.

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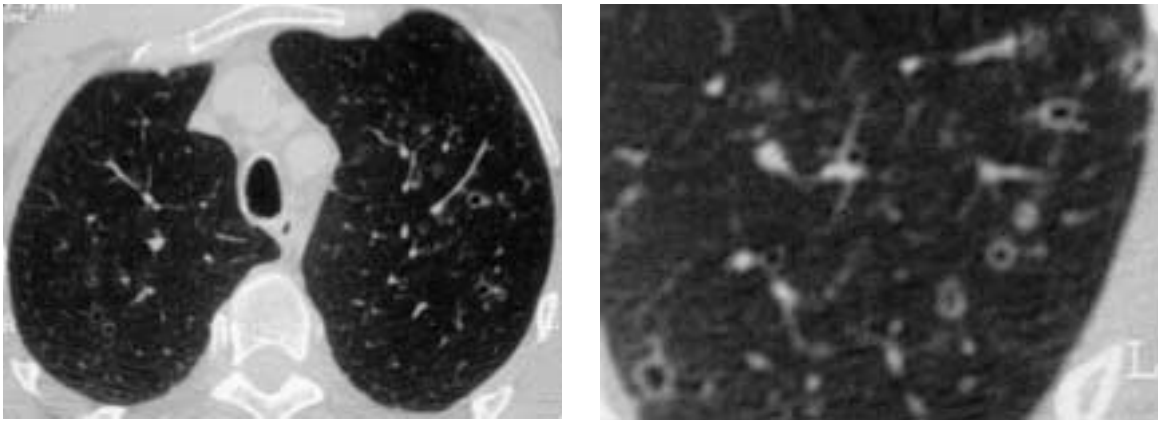

A B

Figure 1

A, B: Computed tomography scans of the lungs showing bilateral intrapulmonary "ring-shaped structures".

Three months after intestinal surgery the abdominal computed tomographic scans (CT) were without evidence of local or lymphatic recurrences, but the thoracic CT scans showed "ring-shaped structures" in both lungs. One month later repeat CT scan of the thorax was performed and there was distinct increase of these pulmonary "ring-shaped structures" (figure 1). The chest X-ray remained inconspicuous. Physical examination, laboratory studies, electrocardiogram, echocardiogram and pulmonary function were normal. Magnetic resonance imaging of the brain and bone scintigraphy with 99mTc-MDP excluded cerebral and osseous metastasis respectively.

Bronchoscopy showed a normal bronchial system and the histology of endobronchial biopsies and bronchioalveolar lavage was without evidence of tumour or inflammatory cells.

A left lateral thoracotomy was performed and multiloculated nodules (maximum diameter 0.4 cm) were seen involving the whole lung. A wedge resection of the apical part of the left lower lobe containing multiple nodules was performed. These intrapulmonary nodules were moderately firm. Histological examination of the lesions showed scattered nodules, frequently next to small airways. The cellular infiltrates included lymphocytes, macrophages and histiocytic cells. In some of the nodules small cavities engulfed by macrophage infiltrates were present. In all specimens there was no evidence of bacterial or mycotic infection. The cellular infiltrates showed a positive reaction with anti-CD1a. The final diagnosis was pulmonary Langerhans' cell histiocytosis (histiocytosis X). There was no evidence of metastatic malignant melanoma.

Discussion

In the case presented here, multifocal pulmonary metastasis of a malignant melanoma or a local retroduodenal recurrence via direct invasion of the inferior cava vein were the initially considered diagnoses, but further investigations, including CT scans of the abdomen, showed no evidence of local recurrence. Open-lung biopsy revealed the definitive and unexpected diagnosis of pulmonary Langerhans' cell histiocytosis (histiocytosis X).

Langerhans' cell histiocytosis is an uncommon granulomatous disease of unknown aetiology with several different manifestations: Abt-Letterer-Siwe disease (an aggressive systemic form), Hand-Schüller-Christian syndrome (triad of exophthalmos, diabetes insipidus, and bone lesions), and eosinophilic granuloma (single-organ involvement). Although pulmonary histiocytosis X is not an unusual presentation of the disease, primary involvement of the lungs is unusual, the pulmonary involvement usually being part of a multisystem process [2, 3].

The major trigger of histiocytosis X of the lungs in most patients is cigarette smoking [2, 4]. Langerhans' cells are differentiated cells of monocyte-macrophage lineage that function as antigen-presenting cells. Cigarette smoking causes an increase in Langerhans' cells in the lungs of smokers [4, 5]. Cigarette smoke probably induces recruitment and activation of Langerhans' cells to the lung: through a) direct activation of Langerhans' cells by secreted cytokines, or b) activation of alveolar macrophages by release of bombesin-like peptides from airway neuroendocrine cells, or c) stimulation of the alveolar macrophages by other antigens in cigarette smoke [4]. Recurrence of the disease after lung transplantation supports the view that the primary abnormality lies in the Langerhans' cells or precursor dendritic cells [6]. In animal studies mice exposed to tobacco smoke develop an interstitial granulomatous inflammation similar to pulmonary Langerhans' cell histiocytosis in humans [7]. When tobacco smoking ceases the interstitial granulomatous inflammation return to control levels [7]. Clinical reports also document stabilisation of clinical symptoms and objective radiographic improvement and improvement in lung function after cessation of smoking [8, 9]. Smoking cessation is an essential part of the treatment. In our case the patient had occasionally smoked in the past, but after the diagnosis of malignant melanoma eight years previously, he had stopped cigarette smoking completely. As men-

tioned above when cigarette smoking ceases the major trigger of pulmonary Langerhans' cell histiocytosis is eliminated.

Association of Langerhans' cell histiocytosis with a malignant neoplasm is rare, the most common of which are Hodgkin's disease, non-Hodgkin's lymphoma and acute non-lymphoblastic lymphoma as well as solid tumours, mostly lung carcinoma, breast carcinoma, thyroid carcinoma and central nervous system tumours. In most cases Langerhans' cell histiocytosis predates or occurs concurrently with the associated neoplasm. Only a small number of cases of malignant neoplasms preceding Langerhans' cell histiocytosis have been reported [1]. In patients with a malignant melanoma development of Langerhans' cell histiocytosis in lymph nodes but not in the lungs has been reported [10, 11]. Regarding the pathogenic mechanism of Langerhans' cell histiocytosis in association with malignant neoplasms, two hypotheses have been suggested: the development of Langerhan' cell histiocytosis a) as a reactive response to the malignant neoplasm or b) as a result of the chemotherapy [1, 10, 12]. In the case presented if the development of Langerhans' cell histiocytosis were a reactive response to the malignant melanoma, lymph nodes within the drainage site of the cutaneous malignant melanoma and not in the lungs would be the expected site. In this case pulmonary Langerhans' cell histiocytosis developed after chemotherapy for metastasis of the malignant melanoma. Development of pulmonary Langerhans' cell histiocytosis after chemotherapy has been reported in patients with Hodgkin's disease [12].

Although the exact mechanism is not known, in our case, chemotherapy for metastasising malignant melanoma resulted in the development of pulmonary Langerhans' cell histiocytosis.

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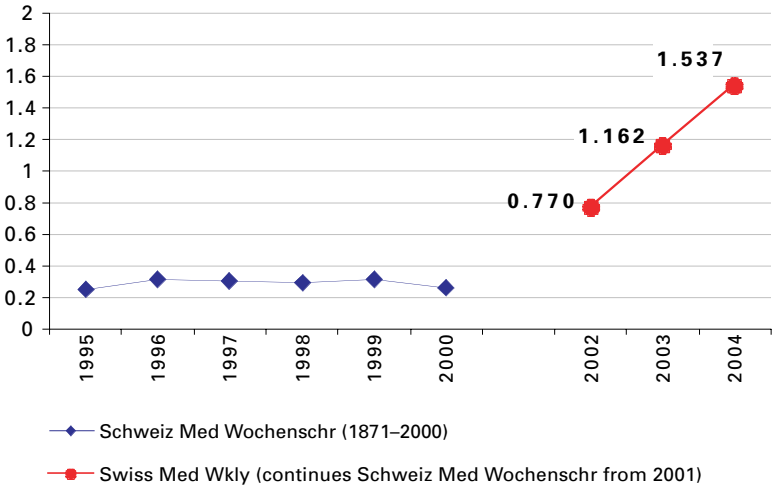

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