Pulmonary vasculitis may obscure large cell lung carcinoma. A case report

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ABSTRACT
Several vasculitic syndromes are recognized as paraneoplastic syndromes of an underlying malignant disease. Most frequently small vessel vasculitis of the skin has been reported. We describe the case of a 62-year-old man with a pulmonary mass due to pulmonary vasculitis. After resection of the pulmonary mass, the patient displayed bone metastasis. Retrospectively, tumor cells were found in the pulmonary mass that had been resected 9 months before.

In this case report the rare association of vasculitis and lung carcinoma is reviewed. Our report indicates that pulmonary vasculitis may obscure the histological findings of lung carcinoma and that in patients with localized pulmonary vasculitis special attention has to be paid to the possible presence of malignant cells.

Introduction
Several syndromes may be associated with an underlying malignant process. These so-called paraneoplastic syndromes can be divided into endocrine syndromes and hematologic syndromes (1). The nervous system may also be involved. Well known examples are membranous glomerulopathy, neuropathies, ectopic hormone production, dermatological abnormalities, collagen vascular disorders and rheumatic diseases (1,2). Vasculitis can also occur as a paraneoplastic syndrome; small vessel vasculitis of the skin is the most common manifestation of a paraneoplastic vasculitic syndrome (3-6).

Churg-Strauss syndrome (CSS) is a special form of vasculitis with asthma, eosinophilia and vasculitis (7). CCS has never yet been reported as a paraneoplastic syndrome with a malignancy of the lung. We recently observed a patient with asthma, eosinophilia and vasculitis coupled with carcinoma of the lung, compatible with a diagnosis of paraneoplastic CSS.

Case report
In November 1996, a 62-year-old male patient was admitted to the hospital because of amaurosis fugax. He had a history of hypertension, 40 years of smoking, and pulmonary embolism after a period of immobilisation in 1984. He underwent an aortobifemoral bypass graft in 1985. After partial obstruction of the prosthesis, he was prescribed life-long anticoagulation therapy.

On admission a stenosis of the left internal carotic artery was diagnosed and an endarterectomy was performed. A routine perioperative chest X-ray demonstrated a mass in the anterior segment of the right upper lobe of the lung, which was confirmed by CT scan. No other abnormalities were found. Postoperative evaluation revealed dyspnea with wheezing on exertion, and pulmonary function testing showed an obstructive pattern. At bronchoscopy no endobronchial abnormalities were seen. Bronchial alveolar lavage showed alveolar macrophages, non-malignant epithelial cells and some granulocytes. Histology of the biopsy revealed reactive inflammatory changes with a focal lymphocytic infiltrate, and in addition alveolar macrophages, foam cells and some fibrosis.

The clinical and radiological evaluations strongly suggested primary lung malignancy and in December 1996 a lobectomy of the upper and middle lobe of the right lung was performed. Histologic features of the macroscopic firm, solid mass showed inflammation of the large, medium and small vessels with occasional total obliteration. Many eosinophilic granulocytes and lymphocytes were present. In the necrotic tissue remnants of blood vessels were seen. Sporadic giant cells were observed.

A histologic diagnosis of vasculitis was made. Since eosinophils and giant cells were present, it was felt that the histologic pattern fitted best with a Churg-Strauss-like lesion. Therefore, the patient was referred to one of us (JWCT) and extensively evaluated (8). No manifestations of systemic vasculitis were documented. ENT evaluation revealed no nasal polyposis or other abnormalities. The bloodfilm showed a normal amount of eosinophils (0.32x10⁹/l normal value < 0.33 x 0/l); C-reactive protein was elevated (20 mg/l, normal value <3 mg/l) and the erythrocyte sedimentation rate was elevated (67 mm/
There were no signs of glomerulonephritis (normal urinalysis, no proteinuria, and normal creatinine clearance). ANCA testing by immunofluorescence and by capture ELISA (8) was negative. No definite diagnosis was made. It was felt that the pulmonary findings of this patient fitted a diagnosis of an incomplete form of limited Churg Strauss syndrome or limited Wegener’s granulomatosis. After recovery from the operation, the patient was in good health without signs or symptoms related to vasculitis and no further treatment was given. The erythrocyte sedimentation rate returned to normal. In September 1997, however, he displayed thrombosis of the left popliteal vein in spite of adequate anticoagulation therapy. Furthermore, he complained of malaise, weight loss, pain in his right thorax at the site of the operation, and arthralgia of his right shoulder and right elbow. Upon physical examination, no new abnormalities were found. Laboratory analysis were suggestive of active Churg-Strauss vasculitis (high C-reactive protein 210 mg/l; normal value < 3, a high erythrocyte sedimentation rate 107 mm/h, and blood eosinophilia 0.70 x 10⁹/l). ANCA tests were negative. An X-ray of the chest showed a triangular mass in his right hemi-thorax at the level of the sixth rib, which appeared to have fractured spontaneously. An incisional biopsy of the right chest wall revealed a tumorous process consisting of a poorly differentiated large cell carcinoma. A skeletal scintigraphy (⁹⁹M-Tc-MDP) showed evidence of multiple metastases, which was confirmed by biopsy. The material that had been

Fig. 1. (a) Overview of an almost totally obliterated vessel; infiltrate, including eosinophils (arrows), resembling a Churg-Strauss vasculitis (haematoxylin-eosin, 100x).
(b) Detailed picture of a vessel. Within the vessel eosinophils and somewhat larger, pale cells are present. The latter resemble swollen endothelial and intimal cells but in fact are tumor cells. This is shown in figure 1c.
(c) A vessel (center) infiltrated and surrounded by cytokeratin-positive tumor cells. These cells are recognizable by their somewhat larger appearance, with larger nuclei and nucleoli than the cytokeratin-positive alveolar type 2 pneumocytes (right, lower area) (cytokeratin 7, immunoperoxidase, 200x).
obtained during lobectomy was reviewed (WT) and it was found that areas with fibrosis and large, atypical cells compatible with a large cell carcinoma of the lung were present, although almost entirely obscured by the extensive inflammatory response (Fig. 1). This was confirmed by positive keratin immunostaining. The process did not involve the pleura and remained distant from the surgical margin. Chemotherapy was planned, but the patient refused and died several days after leaving the hospital. No autopsy was performed.

Discussion

Several vasculitic syndromes are known to occur as paraneoplastic syndromes. In this association small vessel vasculitis syndromes predominate and are mostly found in combination with lympho- and myeloproliferative disorders (2-6). Carcinoma has also been described in relation to small vessel vasculitis syndromes previously reported with lung carcinoma (summarized in Table I). In our case, the initially resected part of the lung showed large cell lung carcinoma almost totally obscured by an infiltrate with vasculitis, necrosis and extensive eosinophilic infiltration with sporadic giant cells. The histological picture fitted best with Churg Strauss syndrome (CSS), since the vasculitic process involved the arteries and arterioles and was accompanied by tissue infiltration by eosinophils and sporadic giant cells. Because the lesions in our patient were limited to the lung, it was extremely difficult to differentiate on histologic grounds between CSS and Wegener’s granulomatosis.

The diagnostic process in patients with pulmonary vasculitis may be facilitated by the finding of autoantibodies against myeloid lysosomal enzymes (13). The finding of proteinase 3 ANCA in these patients suggests Wegener’s granulomatosis, whereas the finding of myeloperoxidase ANCA suggests CSS. Unfortunately, in our patient the screening for both of these antibodies remained negative. The absence of ANCA, however, is compatible with either a diagnosis of a so-called “limited”CSS (8) or “loco-regional” Wegener’s granulomatosis (14).

There is one case report in the literature of an assumed association between CSS and malignancy (15). In this case a melanoma was diagnosed in an asthmatic patient and resected completely. Four years after this operation CSS developed, and one year thereafter metastases were found. In contrast to the previously described case (15), we found an unequivocal relationship between the vasculitis and the presence of malignancy. We would speculate that the underlying mechanisms of this paraneoplastic pulmonary vasculitis may involve an immune complex vasculitis, as in most forms of secondary vasculitis (16). Another possible mechanism could be a neoantigen or tumor antigen which presents at the surface of endothelial cells and initiates a cell-mediated immune reactivity to the vessel wall. Furthermore, eosinophils may be attracted and these cells could release toxic products resulting in vessel wall damage and vasculitis.

From the current case report it is not clear whether the inflammatory reaction of the blood vessels was beneficial for our patient. Vasculitis may cause thrombosis of the vessels which vasculatise the tumor, and the induction of vasculitis has been suggested by Nabel et al. as a treatment modality for malignancies (17, 18). However, since our patient suffered a relentless downhill course, we are not convinced that he benefited much from the vasculitic process.

In conclusion, we observed a patient with pulmonary vasculitis associated with large cell carcinoma of the lung. Despite a strong clinical suspicion of malignancy the carcinoma was initially not detected due to the overwhelming vasculitic inflammatory process. Our case report underscores the importance of considering a paraneoplastic syndrome in patients with vasculitis.

References

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CASE REPORT


