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CASE STUDY

Adenocarcinoma of the lung mimicking inflammatory lung disease with honeycombing

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Adenocarcinoma of the lung mimicking inflammatory lung disease with honeycombing. S. Lantuejoul, T.V. Colby, G.R. Ferretti, P.Y. Brichon, C. Brambilla, E. Brambilla. ©ERS Journals Ltd 2004.

ABSTRACT: Pulmonary adenocarcinoma of the lung and its variants are well-defined entities, since the recent WHO classification of lung tumours. However, scant descriptions have been allocated to associated stromal changes, such as prominent inflammation and fibrosis, which can overshadow a tumoral proliferation and masquerade as a benign reactive process and this has not been recognised as a histopathological variant.

The case of a 72-yr-old farmer who presented a multifocal well-differentiated adenocarcinoma that mimicked honeycomb lung with bronchiolectasis radiologically, on computed tomography scan and histologically at open lung biopsy, is reported. Histological pitfalls in the biopsy were represented by mild atypical cuboidal or columnar epithelial cells lining bronchiolar structures resembling florid bronchiolar metaplasia in a background of extensive fibrosis and inflammation, features that mimicked inflammatory honeycombing. However, histological analysis of the surgical resection of the main lesion, performed because of a clinical alteration of the patient, confirmed the diagnosis of multifocal adenocarcinoma of mixed subtype. A monomorphic proliferation of clear cells, lack of associated ciliated or squamous cells and presence of significant cytologic atypia gave a diagnosis of malignancy.

This case illustrates how inflammatory and fibrotic changes may conceal a correct diagnosis of carcinoma and emphasises the importance of adequate sampling in such cases.

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The last WHO classification of lung tumours subdivides adenocarcinoma into acinar, solid, papillary and bronchioloalveolar variants with the addition of the mixed variant, which is actually the most frequent [1]. This monograph includes relatively little discussion of the stromal changes, which can be particularly prominent in some cases, and overshadow the tumour. Thus, while benign reactive conditions can be misinterpreted as malignancies, a number of malignant lesions can in turn be mistaken as benign and inflammatory when the stromal reaction dominates [2]. The current study reports an example of a multifocal well-differentiated mixed-type adenocarcinoma of the lung, associated with an extensive and inflammatory background mimicking inflammatory lung disease with honeycombing both on the computed tomography (CT) scan as well as on the open lung biopsy. This specific histopathological presentation has not been identified or described as a variant of adenocarcinoma in the latest WHO classification.

Clinical presentation

A 72-yr-old retired farmer, with a past history of suspected tuberculosis treated for 2 months 26 yrs previously, developed an infiltrate of the left lower lobe associated with fever in November 1998. This was interpreted as pneumonia but no clinical and radiological response to antibiotic therapy was obtained. One month later, the chest radiograph and the CT scan revealed other nodular consolidations in the right upper and lower lobes. Physical examination was normal. Laboratory results including blood cell count and erythrocytes sedimentation rate were normal. The bronchoalveolar lavage showed 90% polymorphonucleates but no growth of microorganisms. Immunological analysis exhibited nuclear antibodies positive at 1:320 title. Antineutrophil cytoplasmic antibody and Aspergillus serologies were negative. Fibreoptic bronchoscopy and fine needle aspiration were negative for malignancy. However, culture grew *Aspergillus fumigatus* and the patient was treated with Itroconazole for 9 months from January to October 1999. After two subsequent episodes of fever, antibiotics and steroids were added to the regimen, but only a transient clinical improvement was noted with a decrease at half size of the bilateral consolidations on the CT scan. An open lung biopsy performed in November 1999 showed an inflammatory fibrosis with honeycombing interpreted as inflammatory lung disease due to recurrent infections.

Since all microbiological results were negative, the patient was treated by corticosteroid again with a slight amelioration. However, after several febrile episodes, he was referred to the Dept of Respiratory Medicine of Grenoble Hospital in October 2000. He was in a clinically stable status but presented a slow progression of his pulmonary process on the CT scan, which showed an increase in size of the bilateral

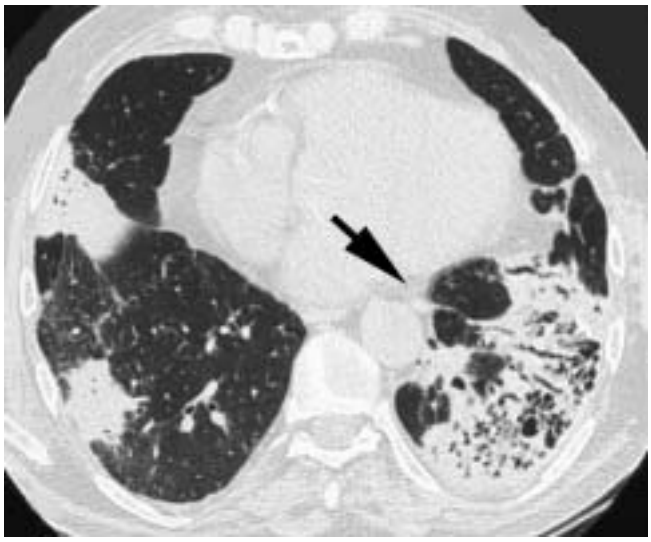

Fig. 1. – Computed tomography scan showing bilateral subpleural condensations in the left lower lobe with honeycombing, bronchiectasis and bronchiolectasis.

subpleural opacities. Furthermore, the left lower lobe condensation presented predominant honeycombing changes, associated with bronchiectasis and bronchiolectasis (fig. 1). No interstitial reticular infiltrates, suggestive for an interstitial lung disease, were noted in the adjacent lung parenchyma. At review of the initial open lung biopsy, malignancy was suspected and a surgical approach for a larger biopsy was decided after a multidisciplinary discussion. A left basilar segmentectomy was performed in December 2000 because of multiple infected cavitations in a condensed lobe, and the patient left the hospital 10 days later. He came back within a week because of a small pneumothorax, which was conservatively managed. Sudden death occurred due to pulmonary embolism 3 weeks later. No autopsy was performed.

Histological findings

At low magnification of the original open lung biopsy, architecture was distorted by diffuse and marked inflammatory fibrosis with apparent honeycombing (fig. 2). Many of

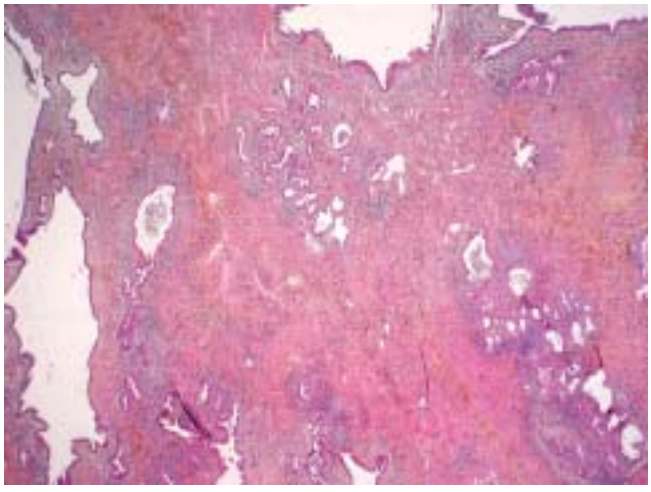

Fig. 2. – Haematoxylin-eosin-saffron stain showing lung architecture with fibrosis and honeycombing.

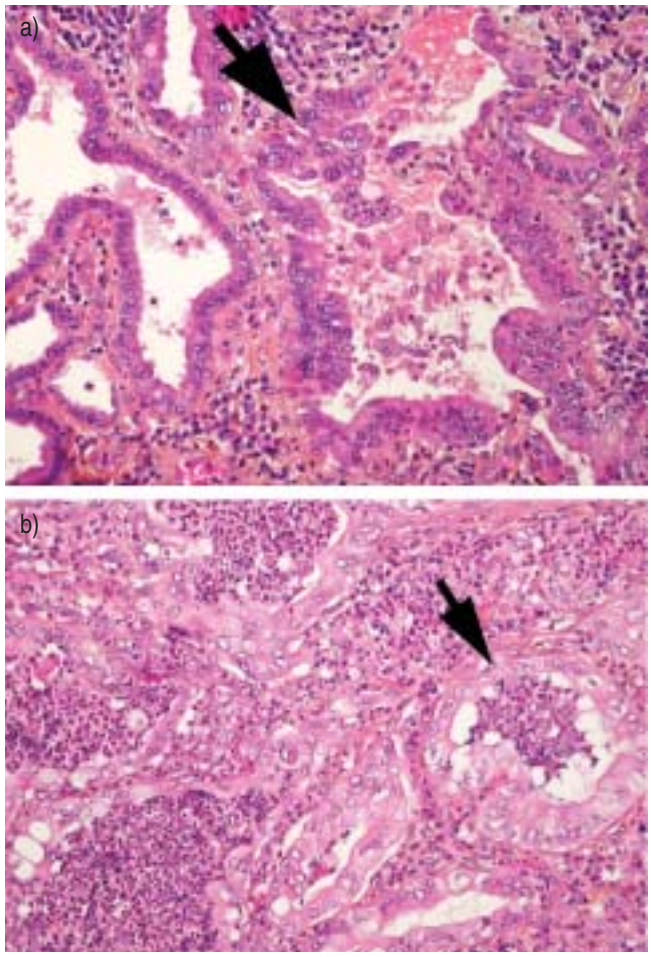

Fig. 3. – Haematoxylin and eosin stains showing: a) bronchioles lined by densely packed atypical epithelial cells, projecting tufts into the lumina (arrow) at higher magnification; and b) overt malignancy in this area, characterised by clear mucinous cells forming acini, pooled by neutrophilic microabcesses (arrow).

the bronchiole-like structures were lined by monomorphic columnar or cuboidal cells with mild atypia, and frequent tufts of crowded growth (fig. 3a). The bronchiole-like spaces were frequently flooded with neutrophils and mucus, and superficially resemble florid bronchiolar metaplasia in a background of inflammation. No microorganisms were identified with special stains. Rare acinar formations lined by mucinous cells and exhibiting frank nuclear atypia were noted at the edge of the biopsy (fig. 3b). Based on these features, the diagnosis of malignancy was strongly suspected. This impression was confirmed upon histological examination of the left lower lobe resection, which shows a predominant and multifocal honeycombing in subpleural location surrounded by areas of alveolar consolidation. Histologically, the same bronchiolar lesions to those observed on the open lung biopsy were found, as well as frank acinar adenocarcinoma. It is mainly composed of clear mucus secreting cells presenting frequent mitotic figures, hyperchromatic nuclei and prominent nucleoli. Some are found isolated within the stroma. At the periphery of fibrotic areas and honeycombing, the neoplastic proliferation exhibits papillary or bronchioloalveolar growth pattern with an abrupt transition to normal alveolar structures. Immunohistochemically the neoplastic cells exhibit a high proliferation index with >20% of the nuclei stained by Ki 67 antibody. Furthermore, a P53 accumulation can be demonstrated in all histological patterns of the

neoplasm. Carcinoembryonic antigen and thyroid transcription factor 1 (TTF1) are not expressed by tumour cells.

Discussion

This study reports a case of a multifocal well-differentiated adenocarcinoma, mimicking honeycombing and inflammatory lung disease both radiologically and histologically. This phenomenon has been previously reviewed and illustrated [2, 3] but it is not well documented in the literature. The radiological presentation was that of stable foci of pulmonary consolidation along with signs of architectural distortion. The differential diagnosis included chronic organising pneumonia, chronic eosinophilic pneumonia, and drug-induced pneumonia, and the absence of response under corticosteroids and absence of hypereosinophilia (blood and bronchoalveolar lavage) provided no support for these possibilities. Chronic necrotising aspergillosis was considered unlikely because of the lack of cavitation. Bronchioloalveolar carcinoma and primary pulmonary lymphoma were also considered unlikely because pulmonary architectural distortion is uncommon in these conditions. Finally, the progression of multifocal radiographical abnormalities beyond 2 yrs, the absence of response to corticosteroids, and lack of support for other possibilities, strongly suggested a neoplastic process. Histological features suggesting malignancy included: the presence of monotonous mucinous cells that were cuboidal or columnar and lacked cilia, the absence of squamous metaplasia, the formation of papillary projections and crowded growth, and the presence of significant atypia. In addition, P53 protein was consistently expressed in all histological patterns and especially by cells lining these pseudobronchiolar formations, in agreement with the P53 accumulation observed in 30% of pulmonary adenocarcinoma and 66% of nonsmall cell lung carcinoma [4, 5]. However, such a P53 accumulation can also be detected in several nontumoral conditions, such as diffuse alveolar damage, as a reactive process leading to alveolar cell apoptosis regardless of a gene alteration [6]. Nevertheless, in the present case, in absence of clearly identified interstitial lung disease on both the CT scan and surgical specimen, this P53 expression was strongly supportive of malignancy.

Bronchiolar metaplasia represents the main histological differential diagnosis. It can occur in various conditions, including radiation and chemotherapy induced changes, reparation processes, viral infections and bronchiectasis. Furthermore, bronchiolar metaplasia and bronchial lumens flooded with mucus and neutrophils, are very commonly observed in interstitial lung diseases presenting a usual interstitial pneumonia (UIP) pattern, including honeycomb lung and interstitial inflammation. Indeed, UIP as well as pulmonary fibrosis in relation with collagen vascular and occupational lung diseases, can predispose to lung carcinoma, its incidence reaching 3–9% in UIP depending on smoking status [7–9].

The type of carcinoma described in the current report probably originates from bronchiolar cells, which differ from Clara cells and exhibit some mucinous features as suggested by their lack of TTF1 expression, contrasting with that of normal pneumonocytes or Clara cells in the vicinity. Nearly 15% of primary pulmonary adenocarcinomas are said to be TTF1 negative, particularly those arising from mucinous bronchiolar cells [10, 11].

There is still much to be understood concerning the pathogenesis of fibrosis and inflammation in cases such as this. The sequential timing of malignant epithelial proliferation *versus* prominent inflammatory fibrosis is a matter of debate. Architectural distortion generated by the tumour could predispose to infections. Otherwise, multiple recurrent infections may be regarded as having played a predominant role in carcinogenesis. Activated neutrophils are said to contribute to the development of lung cancer, since they release superoxide anion and hydrogen peroxidase inducing DNA damage. Neutrophilic myeloperoxidase can convert tobacco smoke procarcinogen benzo(a)pyrene to benzo(a)pyrene diol epoxide, which favours DNA adducts formation [12, 13]. In lung cancer, tumour cells are able to recruit neutrophils, by excreting chemotactic factors such as interleukin-8, these neutrophils favouring tumour cell invasiveness by secreting neutrophilic elastase, a serine protease capable of extracellular matrix degradation. Bronchioloalveolar carcinoma-infiltrating neutrophils can also produce hepatocyte growth factor, which enables proto oncogene c-met activation in tumour cells leading to cancer progression and cell survival [14–17].

In conclusion, the current study presents an unusual case of a well-differentiated and multifocal adenocarcinoma of the lung, associated with diffuse and extensive inflammatory changes and honeycombing, these latter conditions representing pitfalls in the diagnosis of malignancy. In this setting, clinical outcome and radiological findings must be accounted for by both pathologists and clinicians who must be aware of such an unusual presentation of lung adenocarcinoma, whose diagnosis requires large and representative tissue sampling.

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