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Rheumatoid nodule and combined pulmonary carcinoma: topographic correlations; a case report and review of the literature

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Summary. An association between rheumatoid arthritis (RA) and malignancies has been ascertained and patients with RA appear to be at higher risk of lymphoma and lung cancer. The higher risk of the latter malignancy may be related to rheumatoid interstitial lung disease and immunosuppressive therapies.

Herein we illustrate the case of a 59-year-old male smoker affected by RA and treated with cortisone, methotrexate and TNF-α antagonists, who underwent right lower lobectomy for a nodular lesion. On microscopic examination, the lesion consisted of two distinct areas: a central area of fibrinoid necrosis, bordered by histiocytes in a palisaded arrangement, lymphocytes and a 0.4 cm thick peripheral area constituted by a combined small cell anaplastic carcinoma, adenocarcinoma and squamous cell carcinoma. The combination of three histotypes is very rare in such a small tumour. In our case, it may be hypothesized that synchronous, heterogeneous mutations occurred in different type of committed cells or in stem cells, due to the production of cytokines by RA nodule histiocytes and lymphocytes, which are contiguous to the carcinomatous area. Since few studies have evaluated the topographic correlation between tumors and rheumatoid lung lesions, further morphological and molecular studies are needed to clarify this association and the pathogenetic relationship between RA and cancer of the lung.

Key words: Lung, Rheumatoid arthritis, Interstitial pneumonia, Combined carcinoma

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease of unknown aetiology characterized by symmetric polyarthropathy and resulting in joint destruction, significant debility and premature mortality.

An association between RA and malignancies has been ascertained (Gridley et al., 1993; Chakravarty and Genovese, 2004) and patients with RA appear to be at higher risk of lymphoma and lung cancer (Smitten et al., 2008). While the higher risk of lymphoma may be related to a chronic lymphoid stimulation (Geborek et al., 2005), the risk of lung cancer may be due to a series of factors, including rheumatoid interstitial lung disease (Raghu et al., 2004), the immunosuppressive therapies (Bongartz et al., 2006), that are frequently used in RA, and smoking.

We believe that the contiguity demonstrated between lung cancer and RA lesions, which has yet to be fully analyzed, may contribute to understanding of the pathogenetic relationship between the two. To the best of our knowledge, only three such cases (Blodgett et al., 1972; Shenberg et al., 1984; Baruch et al., 2005) have been described in literature. Herein we illustrate the case of a patient affected by RA and treated with cortisone, methotrexate and TNF-α antagonists. During clinical controls, a pulmonary nodule was detected and a histological diagnosis made of combined carcinoma (small cell anaplastic, adenocarcinoma and squamous cell) contiguous to a rheumatoid nodule.

Materials and methods

Case report

A 59-year-old man was admitted to the Thoracic Surgery Unit of Siena University Hospital in April 2008

for the evaluation of an incidental pulmonary lesion, discovered by routine chest radiography. The chest computed tomography (CT) scan revealed a 3-cm pulmonary nodule with well defined margins in the lower lobe of the right lung. The patient's past medical history was significant due to a long history of seropositive RA, treated with high dose corticosteroids and methotrexate, followed by TNF-α antagonists. The patient smoked 10 cigarettes/day for 30 years. The initial evaluation included bronchoscopy, bronchoalveolar lavage and CT-guided transthoracic fine needle aspiration (FNA). The cytological diagnosis, based on FNA, was "small cell cancer with necrosis". The patient underwent right lower lobectomy.

On the basis of the morphological and immunohistochemical findings, a diagnosis was made of combined carcinoma (small cell anaplastic, adenocarcinoma and squamous cell carcinoma), contiguous to a rheumatoid nodule.

The patient was alive and well twenty-five months after surgery.

Methods

The pathological specimens consisted of the right lower lobe and mediastinal lymph nodes.

Representative samples were fixed in 10% buffered formalin and paraffin embedded, according to standard procedures. From each block, tissue sections (4 mm thick) were cut and stained with haematoxylin and eosin. Gram, Grocott, Ziehl Neelsen, PAS, Picro Mallory, and immunohistochemistry were performed on additional sections of the nodular lesions. For immunohistochemical stains the Ultravision Detection System anti-Polyvalent HRP (LabVision, Fremont, CA, USA; Bio-Optica) was employed, using diaminobenzidine (DAB; Dako) as the chromogen. The following antibodies were checked: CK7, TTF-1, p63, Chromogranin A, Synaptophysin, p53, Ki-67, CD68. Polymerase chain reaction (PCR) for Mycobacterium tuberculosis was performed on formalin-fixed, paraffin-embedded tissues.

Results

On gross examination (Fig. 1), a well-circumscribed nodular lesion was detected at the apical segment of the right lower lobe. It measured 2.7x2x2 cm and was located 0.1 cm beneath the pleural surface, which was retracted. The lesion was solid and greyish at the periphery and necrotic and yellowish in the centre.

The pulmonary parenchyma was emphysematous with irregular, prevalently subpleural, areas of consolidation.

At microscopic examination, the nodular lesion consisted of two distinct areas. A central area of fibrinoid necrosis (Fig. 2) without epithelial cells or debris was bordered by sometimes giant histiocytes, in a palisaded arrangement, and by lymphocytes. The peripheral area consisted of a 0.4 cm thick combined carcinoma: small cell anaplastic carcinoma (about 80%), adenocarcinoma (about 15%) and squamous cell carcinoma (about 5%). The neoplastic tissue was intermingled with histiocytes and lymphocytes. The anaplastic component comprised small cells with dark hyperchromatic nuclei and scant cytoplasm, crush artifacts and nuclear molding, and was positive for Chromogranin A, Synaptophysin, TTF-1 and negative for p63; there were numerous mitoses (105/10 HPF) and the proliferation index (Ki-67) was about 80%. The adenocarcinomatous area was formed of tubules and acini lined with TTF1-positive cells which were negative for Chromogranin A, Synaptophysin, and p63. The squamous cell area consisted of nests of cells that were positive for p63 and negative for TTF-1, Chromogranin and Synaptophysin (Fig. 3). The pulmonary parenchyma showed diffuse emphysema and lymphocytic interstitial broncopneumonia associated with follicular bronchiolitis. The mediastinal lymph nodes were not infiltrated by cancer cells.

Gram, Ziehl-Nelsen and Grocott stains were negative for bacterial and fungal organisms, as was

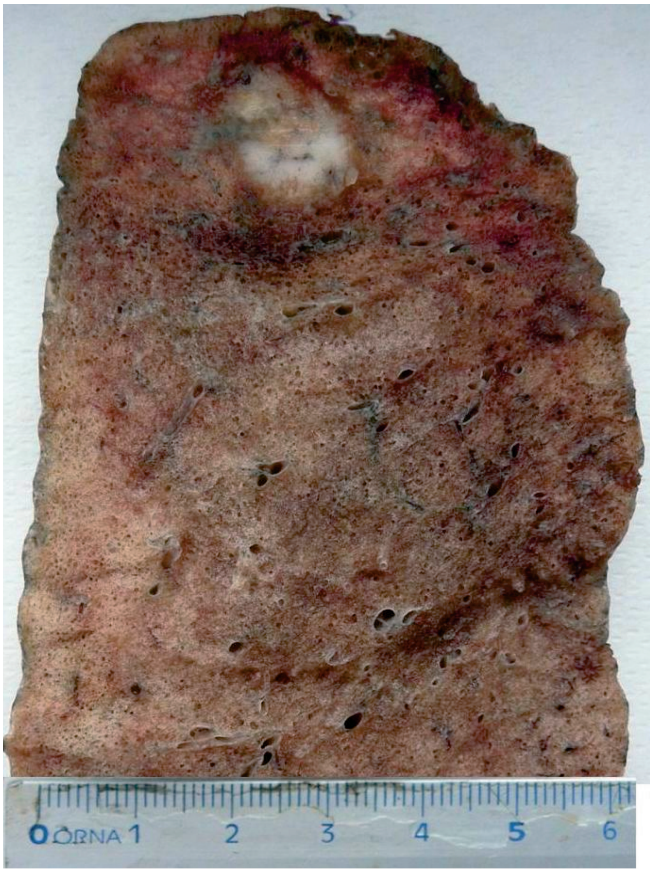

Fig. 1. The nodular lesion is well circumscribed, solid and greyish at the periphery, necrotic and yellowish in the centre. The pulmonary parenchyma is emphysematous but has irregular consolidated areas.

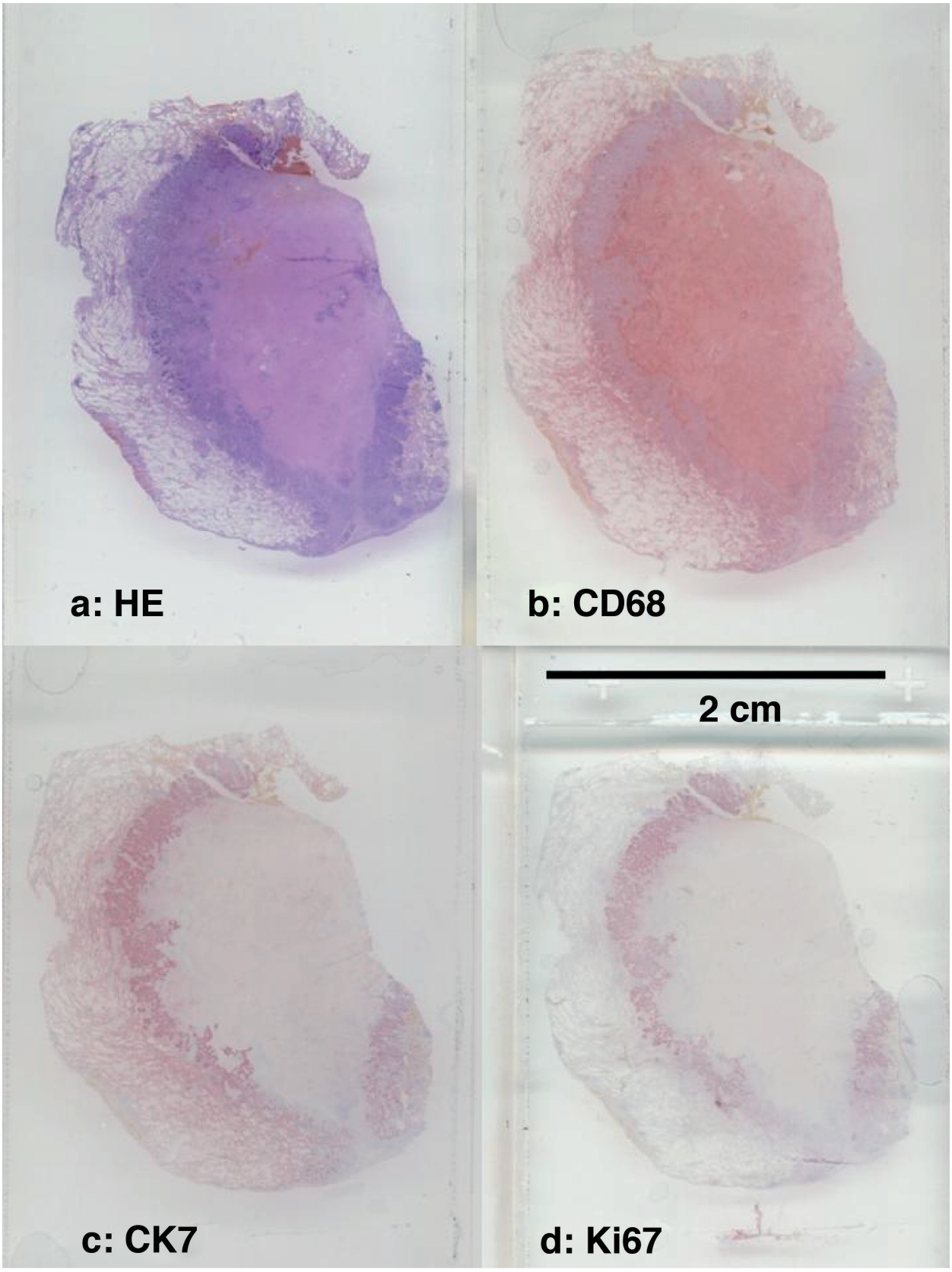

Fig. 2. The central area of the nodule consists of fibrinoid necrosis (**a,** H&E), surrounded by histiocytes (**b,** CD68). At the outer border, a rim of epithelial cells (**c**, CK7) with a high proliferation rate (**d**, Ki-67) is observable.

polymerase chain reaction (PCR) for Mycobacterium tuberculosis.

Discussion

We describe the case of an incidentally detected combined pulmonary carcinoma contiguous to a rheumatoid nodule in a male smoker suffering from RA, treated with steroids, methotrexate and TNF-α antagonists.

Several studies on large series of cases have shown an association between RA and lung cancer (Love and Solomon, 2008), as well as a relationship between smoking and RA disease progression, severity and cancer development (Kallberg, 2008). Smoking is, in fact, the best known risk factor for lung cancer, as well as being the most strongly established environmental risk factor for developing RA, especially very severe RA, characterized by the presence of antibodies to citrullinated protein (anti-cyclic citrullinated peptide, anti-CCP). Therefore smoking is a very important confounder when studying a possible association between RA and lung cancer in smoker patients. A recent retrospective study (Khurana et al., 2008) demonstrated that patients with RA have an increased incidence of lung cancer (OR 1.43) compared to patients without RA controlled for age, gender, smoking and asbestos exposure. Smitten and colleagues (Smitten et al., 2008) reported the results of a meta-analysis in which the relative risk of malignancies in RA patients compared to the general population was expressed by a standardized incidence ratio (SIR), which was 1.63 for lung cancer, suggesting an 1.5-to 3.5-fold increase in risk (Wolfe and Michand, 2007; Setogouchi et al., 2008).

Pulmonary involvement occurs in nearly half of RA patients, in the form of pleuritis, interstitial lung disease

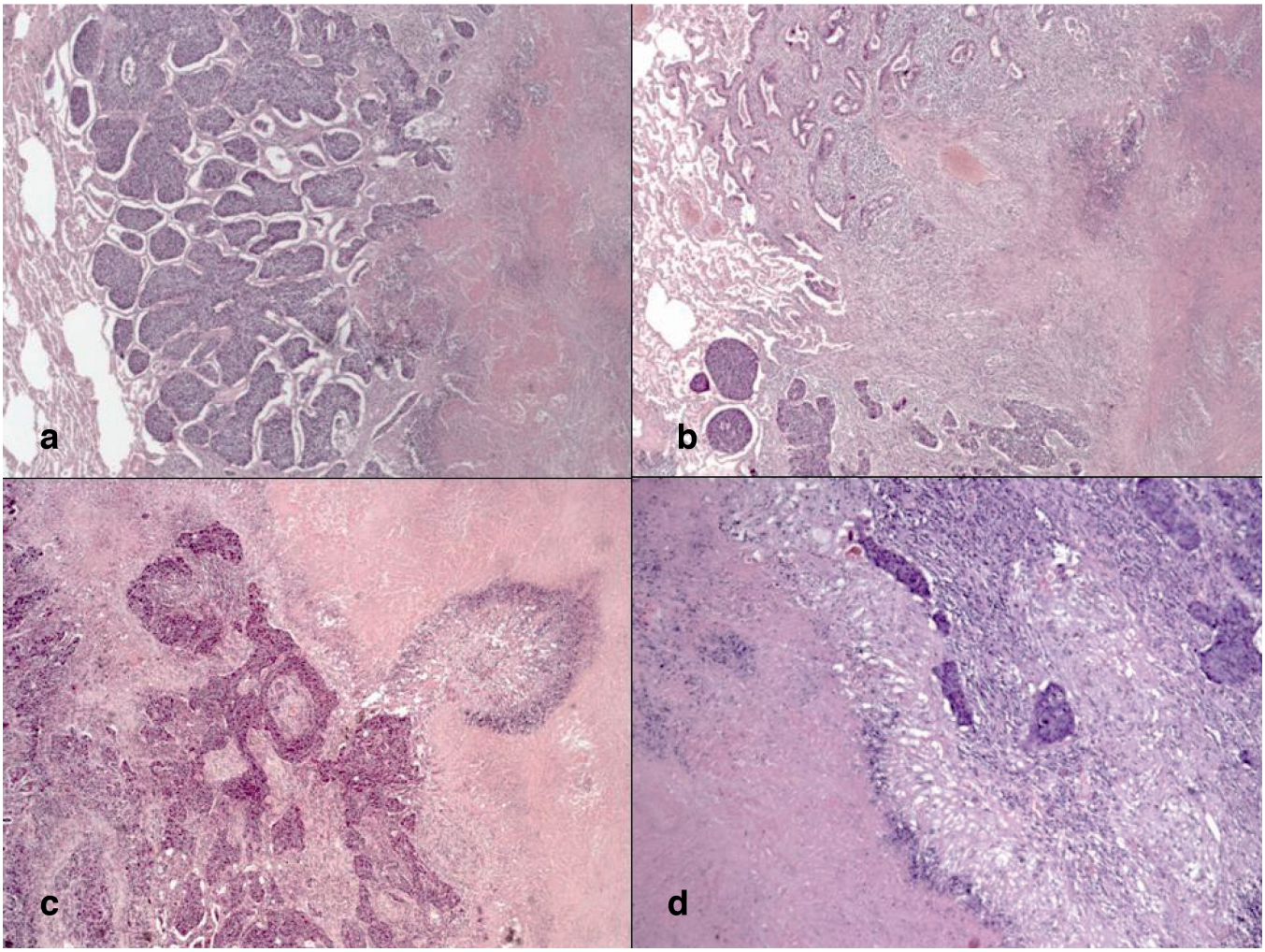

Fig. 3. The perinodular epithelial area is constituted by a small cell anaplastic carcinoma (**a**), closely combined with an adenocarcinoma (**b**), and a squamous cell carcinoma (**c**); histiocytes, in a palisaded arrangement, can be seen between the neoplasia and the necrotic area (**d**). H&E; x 25

and bronchiolitis (Walker and Wright, 1968; Hunninghake and Fauci, 1979), while rheumatoid nodules occur in less than 1% of patients (Shannon and Gale, 1992).

In our case, pathological examination showed lymphocytic interstitial pneumonia and a nodular lesion, measuring 2.7 cm, composed of a rheumatoid nodule with fibrinoid necrosis, lymphocytes, histiocytes and giant cells, surrounded by a 0.4 cm thick neoplastic rim of combined small cell anaplastic carcinoma, adenocarcinoma and squamous cell carcinoma.

The topographic correlation between cancer and rheumatoid lung lesions has only been analyzed in three cases (Baruch et al., 2005). In the first of these cases a RA nodule of 1.5 cm was surrounded by a bronchioloalveolar carcinoma in a male treated with meprobamate, phenylbutazone and indomethacin (Blodgett et al., 1972). The second case dealt with a subpleural nodule of 2.5 cm constituted by conglomerate RA nodules, surrounded by a well differentiated adenocarcinoma with bronchioloalveolar features in a male smoker treated with aspirin, corticosteroids and gold salts (Shenberg et al., 1984). The third case concerned a male smoker with four lung nodules, two of which were RA nodules and the other two were high grade adenocarcinomas with central necrosis (Baruch et al., 2005). In the latter case no contiguity was detected between the RA nodules and cancer, and in the adenocarcinomatous areas the necrosis appeared to be coagulative (neoplastic) rather than fibrinoid.

In our case, the lung cancer was mainly represented by a small cell anaplastic carcinoma, which was combined with adenocarcinoma and squamous cell carcinoma. The combination of three histotypes is very rare in such a small tumour, as shown in daily practice. In fact, combined carcinoma in the lung is more likely to occur in larger tumors in which there is enough time for mutational events to take place, giving rise to different

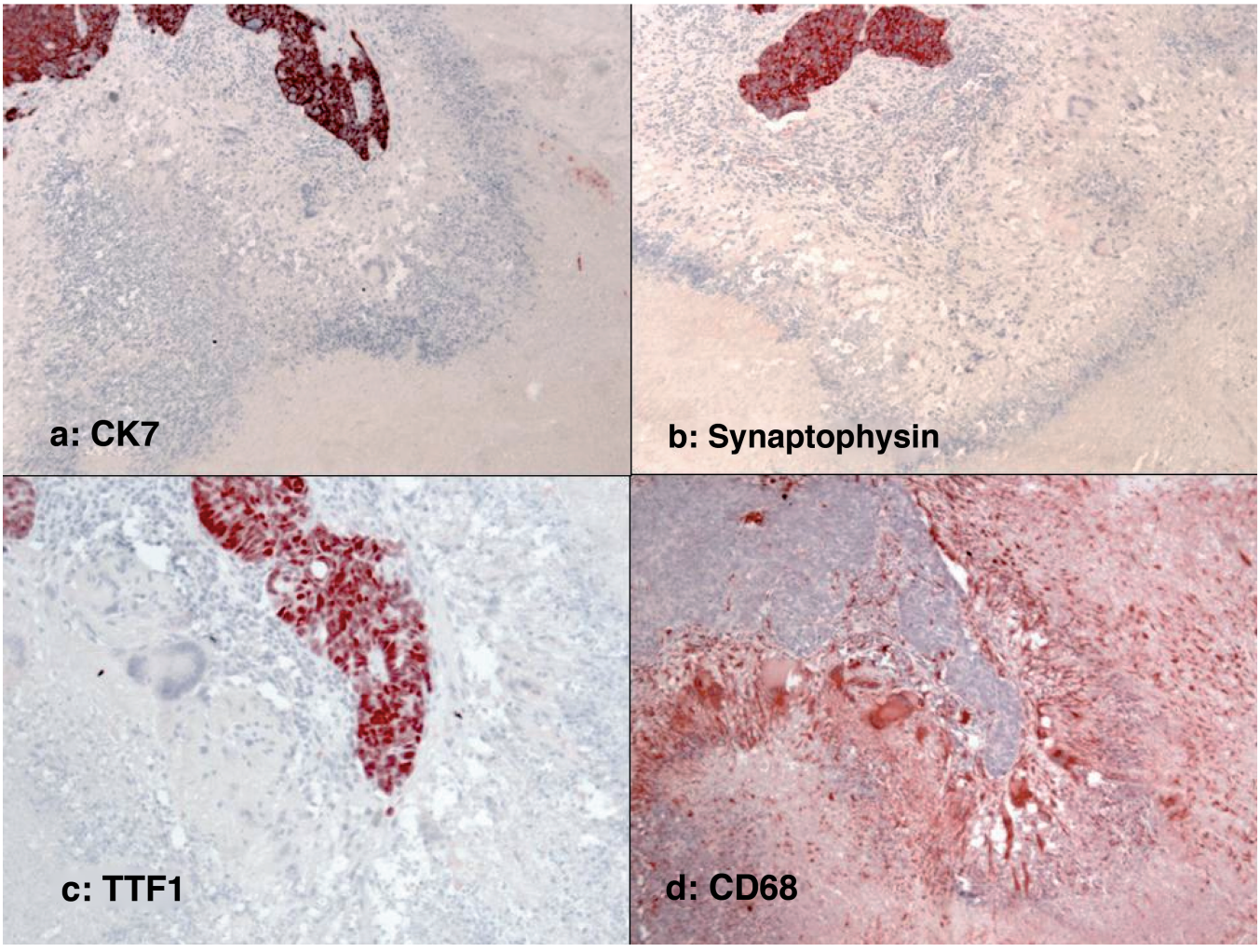

Fig. 4. Note the separation and the contiguity between cancer cells and histiocytes (**a-d**). (**a**, CK7; **b**, Synaptophysin; **c**, TTF-1; **d**, CD68. x 50

tumor histotypes. In our case, the combination of three histotypes may be due to synchronous, heterogeneous mutations occurring in different types of committed cells or in stem cells. A relationship may be hypothesized between the production of cytokines and tumorigenesis on the basis of the contiguity of the carcinomatous areas to the histiocytes and lymphocytes of the RA nodule. On the contrary, the influence of therapy on tumorigenesis should not necessarily be taken into consideration, since different therapies were used at least in the three cases described so far.

In view of the fact that there are only four reports available in the literature, including this one, further studies are needed to clarify the topographical correlations between RA and cancer of the lung. In fact, although it is very unlikely to occur, a random association between the two diseases cannot be excluded. Moreover, accurate morphological and molecular studies might be of help in elucidating the relationship between rheumatoid interstitial lung disease and cancer.

It is important for clinicians to state the differential diagnosis of a solitary pulmonary nodule in a patient with RA. Histologic evaluation is mandatory in all such cases in order to rule out a malignancy, due to the fact that pulmonary carcinoma and a rheumatoid nodule may share the same clinical and radiological features (Voulgari et al., 2005).

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