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Polishing surgical metal pieces, granulomatosis and mineralogical analysis

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Abstract. This report describes the case of a 44-year-old man with pulmonary nodules whose histological analysis initially suggested tuberculosis. The Mycobacterium tuberculosis (MT) culture was negative and a questionnaire revealed a professional activity of brushing and polishing surgical instruments without any protection for 7 years. A mineralogical analysis by optical and electron microscopy was performed on both a healthy lung tissue biopsy and a lung nodule in a paraffin block. Electron microscopy analysis revealed the presence of metal particles (iron oxide, titanium oxide, aluminum oxide and steel) in both samples. This study suggests that mineralogical analysis combined with a questionnaire on dust exposure could help redirect the diagnosis of a dust-related disease. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 166-170)*

Key words: sarcoid-like granulomatous disease; mineralogical analysis; occupational disease

Introduction

Whenever granulomatosis including occasional necrosis is detected, if test results for bacterial infections are negative, a diagnosis of sarcoidosis may be put forward. The cause of this disease remains unknown (1) but is likely to depend on both genetic and environmental factors (2, 3). In recent years, the hypothesis that pulmonary dust deposition may be partly responsible for sarcoidosis has gathered momentum (4, 5). However, standard anatomopathological analysis does not enable medical staff to determine either the presence of particles smaller than 0.4 microns, nor to know their chemical composition. Through the use of appropriate equipment, such as electron microscopy coupled with energy-dispersive X-ray (EDX) analysis, it is possible to detect micro- and/or nanoparticles in pathological tissues (6, 7) and thus suspect a possible link with different types of environmental and occupational exposure. In particular, the detection in healthy lung tissue of an overload made up of identical particles such as those identified in inflammatory lesions can be an additional argument for a causal relationship between exposure and disease (8). The case presented here illustrates this scenario, by highlighting on the one hand how mineralogical analysis may reveal the presence of similar inorganic particles in both unaffected lung tissue and granuloma, and on the other hand how a detailed interview of the patient can unveil an occupational exposure to metallic dust particles that was until then unknown.

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Clinical case

In 1995, Mr. P., born in 1967, underwent a left cervical lymph node dissection for lymphadenopathy, which showed a nonspecific inflammatory reaction. In April 2011, during a coughing episode, rare lung micro-nodules were discovered, the largest one measuring 13 mm. The results of an endoscopy proved to be negative for the biopsy and the MT culture. The PET scan showed a moderate positive uptake of two nodules and a positive uptake of a salivary gland. Given the excavation of the larger nodule, the patient underwent a resection of the nodule via thoracoscopy in January 2013. The anatomopathological examination showed epithelioid and giant-cell granulomatous inflammation, a caseous necrosis suggesting primarily a tuberculosis which was then discussed. The search for MT in cell culture was however negative, which could have led the diagnosis towards sarcoidosis. Questioning the patient more thoroughly with a specific questionnaire revealed an occupational exposure to inorganic dust: the patient used to brush and polish surgical instruments without any protection from 1989 to 1996. This information led medical staff to take advantage of the thoracoscopy to make a lung parenchyma biopsy on healthy tissue in order to carry out a mineralogical analysis on it. Furthermore, an *in situ* analysis of biopsied granulomatous lesions was also proposed. The biopsy of lung parenchyma was prepared by a filtration-digestion method (9), while the pulmonary nodule in paraffin block was subjected to a standard *in situ* method of analysis (7). Optical and transmission electron microscopy (TEM) analyses were performed on both samples. The optical microscopy observation with natural light of *in situ* histological slides showed the presence of granulomas with giant multinucleated cells (Figure 1a) and highlighted previously unreported opaque particles accumulated especially around blood and lymphatic vessels (Figure 1b). At a higher magnification, one could see that most particles had a diameter smaller than 5 µm and that they were grouped in clusters (Figure 1c).

The microanalysis diagram performed *in situ* on 200 contiguous particles, in the pulmonary granuloma biopsy (Figure 2) showed that the most widely represented types of particles were silicates (29%) and titanium oxide (27%). Next on the list were iron oxides (18%), while silica and steel particles were found in smaller proportions (6 and 4%).

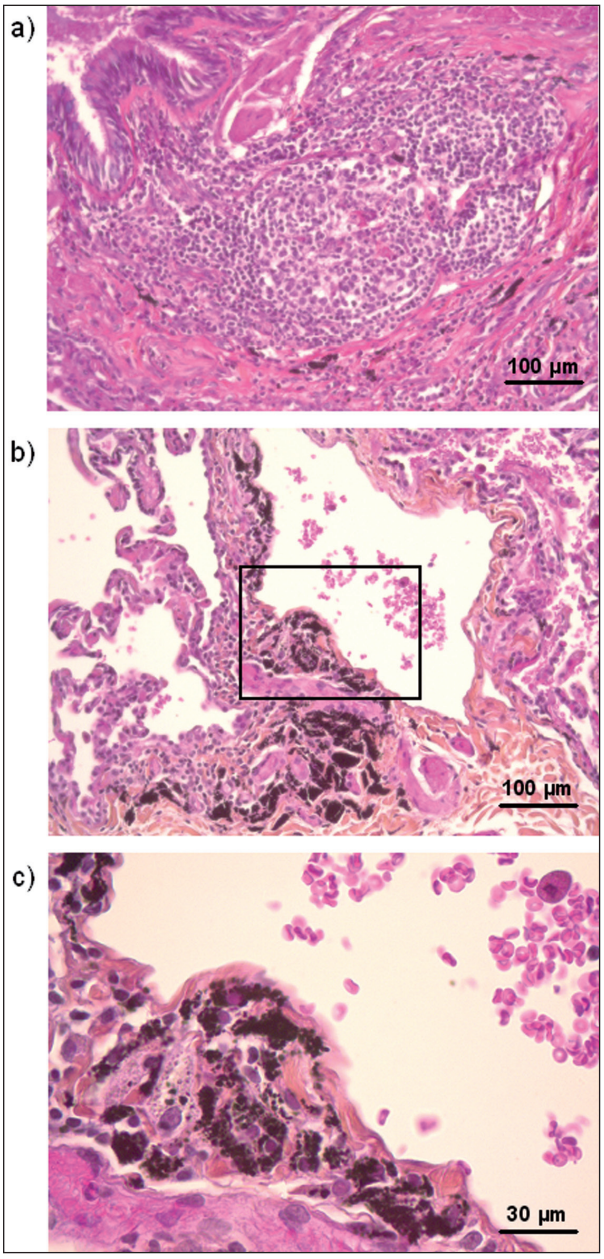

Fig. 1. Light microscopy photographs of in situ histological section of the lung node biopsy, HES colored and at magnification to x200 (a and b) and to x630 (c). The first picture is a granuloma with multinucleated giant cells (a). Both following showed the accumulation of opaque particles grouped in clusters (b and c)

Figure 3 (a, b), which represents TEM pictures of the *in situ* histological section of the pulmonary granuloma biopsy, highlights the presence of particle clusters trapped inside a cell. The microanalysis of

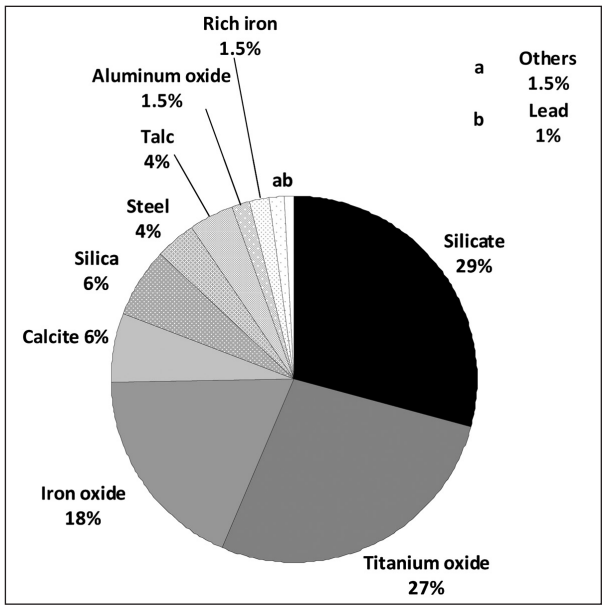

Fig. 2. In situ microanalysis diagram performed on 200 particles from the lung node biopsy

one of these smaller than 0.5 µm multiple-particle clusters showed that it was mainly composed of titanium oxide particles (Figure 3c, d).

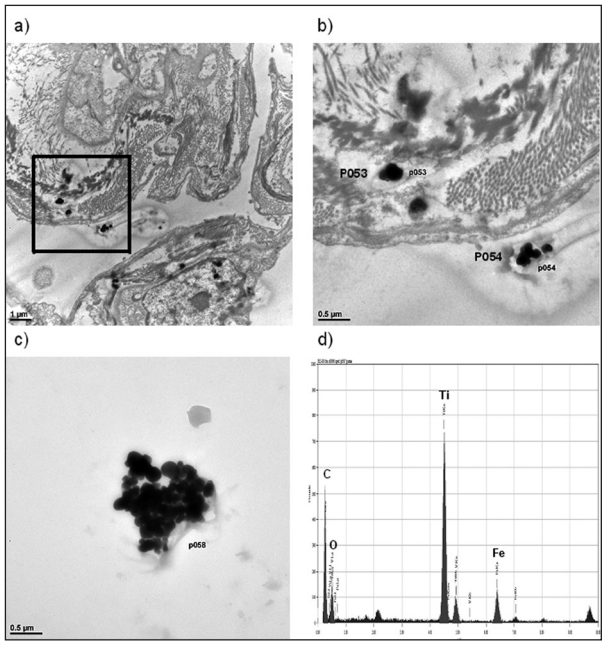

Fig. 3. Transmission electron microscopy photography of histological section of the lung node biopsy at magnification to x10000 (a) and to x30000 (b). P053 and P054 are two particles classified as titanium oxides (b). Photography of a particle cluster at magnification to x30000 issued of the histological section of the lung node biopsy (c) and the corresponding EDX spectrum (d)

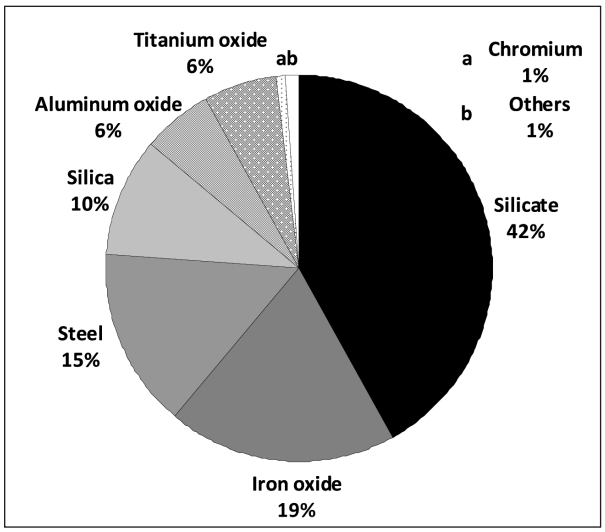

Fig. 4. Microanalysis diagram performed on 200 particles from the digested healthy lung parenchyma

Furthermore, the microanalysis of 200 contiguous particles, taken from the digested pulmonary parenchyma, showed (Figure 4) that most of the particles were silicates (42%) and iron oxides (19%). Silica (10%) and some metallic particles such as steel (15%), aluminum oxide (6%) and titanium oxide (6%) could also be identified.

Discussion

Pulmonary granulomatosis may occur in response to a variety of infectious agents and to the inhalation of both organic and inorganic materials (10). In most cases, the search for a specific causative agent likely to bring about the reaction of granulomatous tissue is difficult. In the present case, after having excluded an infectious agent and on the basis of the patient's occupational history, exposure to one or more materials from his professional activity appeared liable to have been involved in the development of a sarcoid-like granulomatous reaction. The inhalation of metal dust may lead to an inflammatory reaction followed by a pulmonary fibrosis the severity of which depends on the fibrogenic potential of the agent and on some host characteristics that hitherto remain poorly understood (11). This is the case of aluminum whose effects on the lungs are controversial and suspected to be fibrogenic (12).

We have built a TEM mineralogical analysis database on pulmonary parenchyma from a series of subjects who had not been infected with severe lung pathology. This database was set up from autopsies conducted by the Lyon Institute of Forensic Medicine. Out of the 28 samples (i.e. 2,800 particles analyzed), the levels of silica, titanium oxide, aluminum oxide and steel were respectively 7%, 3%, 1% and <1% (results not shown here). These data collected on healthy subjects has enabled us to make useful comparisons with the patient concerned here. Silica, which reached 10% in the healthy lung parenchyma of the patient (Figure 4), could have a role in the development of a sarcoid-like granuloma as discussed in the literature (13). The titanium oxide concentration was two-fold greater than in our reference population; the aluminum oxide content was six times greater; and steel particles reached 15%, although being almost entirely absent in the reference population. The most striking result was the presence of a large number of titanium oxide particles found in the *in situ* analysis of the pulmonary nodule biopsy (27%). The chemical nature of these particles suggests that they came from the patient's occupational activity of polishing surgical instruments without any protection for a period of 7 years. Metallic implants such as those that the patient may have manufactured in the 1990s were (and still are) mainly composed of stainless steel, cobalt-chromium and titanium-based alloys (14). Titanium dioxide is used as a component of joint prosthesis, in particular for the hip and the knee (15). The titanium oxide particles found in both the lung nodule and in the healthy lung parenchyma (Figures 2 and 4) probably resulted from the abrasive wear of parts of polished prosthesis. While the pathological effects of an occupational exposure to this substance have been debated, our case tends to be consistent with Redline *et al.*'s pioneering hypothesis (16) that titanium could possibly induce a pulmonary granulomatous reaction.

Since the 1970s, total hip replacement with an alumina-on-alumina bearing has been developed in order to minimize debris and the occurrence of osteolytic lesions (17). This could be an explanation for the presence of aluminum oxide particles in the healthy lung parenchyma (Figure 4). Another (non-exclusive) explanation could be the use of corundum (Al_2O_3)-coated abrasive belts in arthroplasty or polishing activities. Some studies show that exposure to aluminum particles can cause lung diseases such as sarcoid-like granulomatosis (18, 19).

In 1998, Newman (20) discussed the role of metallic dust inhalation in the onset of sarcoidosis. His review of published studies showed that the granuloma formation could result from the inhalation of certain metals such as aluminum, barium, beryllium, cobalt, copper, gold, rare earth (lanthanide), titanium and zirconium, which have antigenic properties. We have recently published a clinical case showing a type of sarcoid-like granuloma in a person exposed to steel dust, and to a lesser extent, to alumina dust, during her leisure activity of renovating furniture by sanding (21). Newman (20) suggested that clinicians adopt a systematic approach for conducting surveys on occupational and environmental history of patients so as to be able to link exposure to metals and an idiopathic disease.

Conclusion

In the case presented here, the fact of finding steel, titanium oxide and aluminum oxide particles (in higher proportions than in healthy individuals) in both healthy lung parenchyma as well as in granulomatous lesions, supports a causal link between the patient's occupational activity and his sarcoid-like granulomatous disease. Combining the patient's occupational history record and histological and mineralogical analysis allows medical staff to suspect a pulmonary granulomatosis diagnosis in relation to inorganic dust exposure. This conclusion may thus open up two different questions: 1) How many histologically confirmed "sarcoidosis" diagnoses would lead to analogous conclusions on the possible role of inorganic particles in the formation of the granuloma if a thorough exposure questionnaire were completed by the patients and a mineralogical analysis of the tissue were conducted? 2) To what extent does redirecting a sarcoidosis diagnosis towards a sarcoid-like granulomatous reaction question the nosological boundaries of sarcoidosis?

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