CASE REPORT

Pulmonary intravascular talcosis mimicking miliary tuberculosis in an intravenous drug addict

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SUMMARY

Pulmonary foreign body granulomatosis following intravenous administration of medications meant for oral use among drug addicts has been occasionally reported. This condition is often misdiagnosed because of its rarity, but rather due to its similarity to other pulmonary diseases that are more common. Here we report a case of pulmonary intravascular talcosis mimicking miliary tuberculosis in a young male intravenous drug addict from North-Eastern Estonia, known as a hotspot for tuberculosis and drug misuse. The condition was caused by intravenous administration of crushed tablets of diphenhydramine, but miliary tuberculosis was misdiagnosed on patient's demographical, clinical and radiological grounds and a decision to start treatment with four first-line antituberculosis drugs followed. The current report refers to the importance of considering rare causes of pulmonary disseminations with attempts to identify the causative agent and warns against the use of antituberculosis treatment without confirmation of microbiological diagnosis of tuberculosis.

BACKGROUND

Pulmonary talcosis, a form of pulmonary foreign body granulomatosis (PFBG), can occur in drug addicts as a result of intravenous injection of oral medications.^{1–4} The condition has been termed as intravascular talcosis (IT),³ to differentiate it from disorders arising from exposure to inhalational talc, such as simple talcosis,^{5,6} progressive massive fibrosis,^{5–7} talcosilicosis² and talcoasbestosis,² often with pleural disease.⁶

IT may lead to significant lung fibrosis^{1,2} and pulmonary hypertension (PH).^{1,3,8} Moreover, it is often misdiagnosed³ despite some awareness of PFBG in drug addicts.⁹ Numerous conditions like sarcoidosis¹⁰ or tuberculosis (TB)¹¹ can mimic IT, because of the similarity of clinical and radiological findings. In specific circumstances, consideration of certain misdiagnostic alternatives like TB can be fuelled by regional, patient's social status—or HIV infection-related prejudice. In this context, we present a case of a drug addict with pulmonary IT caused by intravenous use of mashed tablets not only mimicking but also resulting in an initial mis-treatment of miliary TB.

CASE PRESENTATION

A 24-year-old male intravenous drug misuser with HIV and hepatitis-C infection, both diagnosed 11 years earlier, was referred to a local outpatient clinic in North-Eastern Estonia, an area with a particularly high incidence of HIV infection and

TB. The patient was on highly active antiretroviral treatment. He was a cigarette smoker for at least 10 years and administered intravenous heroin, amphetamine and methadone. At least during the past 2 years, he also injected crushed tablets of diphenhydramine (Dimedrol 50 mg, Russia), meant for oral administration, twice a week.

The patient was completely asymptomatic, but as his chest X-ray revealed bilateral peribronchovascular small nodules over the lungs (figure 1A), he was hospitalised for further investigations. Physical examination and laboratory tests revealed mild anaemia (haemoglobin content 106 g/L) and oedema on his right leg resulting from self-administration of the drugs. High-resolution HRCT demonstrated diffuse bilateral nodules (figure 1B), which were interpreted as suggestive of disseminated (miliary) TB. Bronchoscopy revealed mild endobronchitis, but no microorganisms, including mycobacteria, were cultured from the bronchoalveolar lavage fluid. Sputum, blood and urine samples were negative for *Mycobacterium tuberculosis*; also, the interferon- γ release test (QuantiFERON-TB Gold, Qiagen, Hilden, Germany) result was negative. The diagnosis of miliary TB was made based on the patient's history and radiological findings and anti-TB treatment with isoniazid, rifampicin, pyrazinamide and ethambutol was initiated.

None of the follow-up HRCT scans made after 2 and 7 months, respectively, of treatment demonstrated any changes. A misdiagnosis was suspected, the anti-TB treatment was discontinued and the patient was referred to a university hospital for surgical lung biopsy (SLB). Video-assisted thoracoscopic SLB was performed and morphological examination of the lung tissue revealed foreign body granulomas (figure 2A, B). These findings were considered confirmative of PFBG. Since numerous organic and inorganic substances^{3,12–14} have been reported to induce PFBG, scanning electron microscopy (SEM) and elemental analysis were performed to identify the nature of the foreign material in SLB. The foreign substance had a layered structure and elemental composition, which were very alike to talc (figure 2C, D). The patient had routine recovery from SLB, but after 1 year follow-up, his radiographic findings surprisingly remained unchanged despite continuation of smoking and intravenous Dimedrol abuse (figure 1C). No signs of PH were revealed on transthoracic echocardiography.

OUTCOME AND FOLLOW-UP

Pulmonary IT is rare and, due to its radiological similarity to other more common diseases, is often

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Figure 1 Radiological findings of the chest of a young male intravenous drug addict from North-Eastern Estonia with intravascular talcosis. Patient's first posteroanterior chest X-ray from December 2011 showing bilateral diffuse peribronchovascular, but not paraseptal small (<2 mm) nodules throughout the lungs (A). The patient's first high-resolution HRCT scan from December 2011 shows bilateral diffuse centrilobular small nodules throughout the lung fields with a tree-in-bud phenomenon and mild upper lobe paraseptal emphysema. There are neither conglomerate masses nor enlarged lymph nodes (B). The patient's HRCT scan 1 year later reveals no changes (C).

a misdiagnosed medical condition, which can occur in drug addicts using intravenously illegal or oral medications. Lung biopsy and a detailed analysis of the granulogeneous material are mandatory to establish the correct diagnosis and to avoid mistreatment, especially in the area of high regional prevalence of TB and MDR-TB.

DISCUSSION

This is the first report of SEM-confirmed pulmonary IT caused by administration of crushed tablets of diphenhydramine (Dimedrol) that was initially misdiagnosed as miliary TB and mistreated with a first-line drug regimen as miliary TB for 7 months. This misdiagnosis most probably occurred due to the pressure by patient-related and regional prejudice and because the test results not indicating the presence of *M tuberculosis* were overlooked. Apart from talc, oral medications may also contain other water-insoluble fillers and binders like cellulose,^{13 14} methylcellulose,³ crospovidone³ and titanium dioxide.¹² All water-insoluble particulate substances reach the lungs, which act as a capillary filter. The repeated embolisation results in accumulation of the foreign material in the pulmonary vasculature and subsequent deposition into the perivascular tissue, causing a body-specific giant cell reaction.^{2 3 8} This reaction, along with direct intravascular deposition of the foreign material, is the most probable cause of PH in these patients.³ In our patient, as the foreign material was deposited in the perivascular tissue and was not present within the arterial lumen, there was no PH and right heart overload.

As several foreign materials can cause a similar micronodular pattern of PFBG,^{3 12 13} the exact causative agent could only be determined by SLB. Typically, in SLB sections of patients with pulmonary IT, fine, birefringent, needle-shaped talc particles can be seen inside the giant cells along with perivascular and

peribronchial fibrosis.^{2 15} This observation has often been considered sufficient for the diagnosis of IT provided a suitable history of exposure exists. However, in parallel with water-soluble narcotics (heroin, amphetamine and methadone solution), our patient injected intravenously crushed diphenhydramine tablets (Dimedrol, Russia), which had not previously been reported as causative of IT. Diphenhydramine (ATC classification code R06AA02) is a first-generation antihistamine with anticholinergic, antitussive, antiemetic and sedative properties and has mainly been used to manage allergic reactions, such as allergic rhinitis, conjunctivitis, urticaria and pollinosis. Diphenhydramine has also been used as an antiemetic agent in vertigo, nausea and Meniere's disease.¹⁶ However, it is used recreationally as a deliriant, as a potentiating agent for alcohol and opiates¹⁷ and causes euphoria and hallucinations, which are all reasons why drug addicts use it. Dimedrol tablets contain talc, lactose, starch and stearic acid as excipients, and since it was the only talc-containing drug that our patient repeatedly injected, we can assume that Dimedrol served as the major cause of his IT. Although Dimedrol is still widely in use, until now there are no reports describing diphenhydramine-containing medicines as causatives of PFBG. Methadone solution (Nycomed, Põlva, Estonia), which was also frequently used by our patient, does not contain insoluble components. Distinctly, intravenous use of crushed methadone tablets is known to cause pulmonary IT.^{1 2}

Pulmonary IT should thus be suspected in patients who have a history of drug addiction.^{1 3 8 13 18} It usually affects men in the fifth decade. Main symptoms include cough and exertional dyspnoea, but patients can be completely asymptomatic, as was the case with our patient. Therefore, a radiological finding is essential. HRCT gives a clue of talc granulomatosis showing small diffuse centrilobular nodules, conglomerate masses,

Figure 2 Analyses on histological sections of surgical lung biopsy. H&E-stain staining (magnification $\times 100$) shows diffuse as well as confluent perivascular foreign body granulomas (arrowhead) with foreign body giant cells and surrounded by mild fibrosis (A). Under polarised light, birefringent crystals (arrowhead) are seen (magnification $\times 100$) (B). Scanning electron microscopy (SEM) image (magnification $\times 1000$) showing heavier particles in lung tissue (arrow) (C). SEM imaging of samples was performed on a variable pressure Zeiss EVO MA15 SEM. Electronic images were taken using uncoated samples, a backscattered electron detector and variable pressure mode. Extra high voltage was adjusted at 20 keV. Elemental analyses performed using an Oxford X-MAX energy dispersive detector system and AZTEC software revealed matter matching talc with sufficient accuracy (D). SEM settings were equal to those used for imaging.

diffuse ground-glass opacities and lower-lobe panlobular emphysema.^{2 15 18} In our present case, the HRCT scan showed only diffuse centrilobular nodules with no conglomerate masses and no remarkable emphysema. Diaz-Ruiz *et al*¹³ reported a case of cellulose granulomatosis of the lung in an HIV-positive drug addict. Similarly to that in our case, the chest HRCT showed only diffuse micronodular infiltrates, but histologically, the foreign body granulomas were related to 20–50 μm long fibre-like particles inherent to cellulose.¹³ In contrast, talc crystals tend to be more needle-shaped and smaller (2–17 μm long).¹³ Hence, as several foreign materials can cause a similar micronodular pattern of lung granulomatosis,^{3 12–14} the exact causative agent can be determined only by lung biopsy.

Pulmonary IT is often underdiagnosed or misdiagnosed because of the similarity of clinical signs and HRCT findings of miliary TB, sarcoidosis, pneumoconiosis, carcinomatosis and histoplasmosis.¹¹ Nevertheless, one cannot exclude the presence of true miliary TB even in patients already having drug administration-related pulmonary granulomatosis. Wong *et al*¹¹ reported a case of coexisting TB and PFBG. In that case report, however, TB was diagnosed based on radiological findings only and PFBG was diagnosed supporting by the finding of birefringent material from transbronchial biopsies. Neither SLB nor a structural analysis of the granulogenic agent was performed. The well-known higher prevalence of TB among drug addicts

and HIV-positives¹⁹ may create pressure on the clinician to start anti-TB treatment in patients presenting with radiologically visible miliary shadowing. In line with this, the context of high prevalence of TB in Estonia together with the particular medical records of our patient (HIV-positivity, drug addiction) compelled the initial misdiagnosis of miliary TB regardless of the negative bacteriological samples and interferon- γ release test, followed by the start of a respective mistreatment. In addition, the absence of response to treatment within 7 months was initially interpreted as being caused by multidrug-resistance, which is also characteristic of Estonia and also of drug addiction and HIV-positivity.¹⁹ Nevertheless, regardless of such coercion, this kind of misconduct must be avoided, especially in conditions of high prevalence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB. Instead, a more precise diagnosis of the pulmonary lesion is necessary.

The most common radiological findings in miliary tuberculosis include diffusely distributed small 2–3 mm nodules along with intralobular and interlobular septal thickening²⁰ with slight lower lobe predominance. The nodules usually disappear within 2–6 months after treatment.²⁰ In our patient, the HRCT stayed unchanged with anti-TB treatment, and therefore the patient was referred for SLB. Sarcoidosis, as second relatively common disease, was the main suspicion after anti-TB treatment failure, as it has been the case also in former reports.^{10 11}

There is no specific treatment for pulmonary IT. Some acute forms of fibrosis, which lead to acute respiratory failure, are treated with corticosteroids, but the overall opinion is that the medical treatment has no benefit.^{2 8 21} Lung transplantation has been considered as a more promising alternative approach.²² The best way to avoid disease progression is to stop drug misuse and smoking. In our patient, the radiological finding remained stable, during 1 year of observation from the first X-ray in December 2011 to the last X-ray in December 2012, despite continuing the use of illegal drugs and smoking.

Learning points

- This case warns against the use of anti-tuberculosis treatment without confirmation of the microbiological diagnosis of tuberculosis.
- Pulmonary intravascular talcosis can mimic many other pulmonary diseases that are more common. Therefore, a more precise diagnosis of the pulmonary lesion is necessary.
- As several foreign materials can cause a similar micronodular pattern of lung granulomatosis, the exact causative agent can be determined only by lung biopsy.
- Scanning electron microscopy-based analysis with confirmation of the nature of the foreign material by elemental analysis is provided.

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Contributors AA drew the concept of the studies performed on the patient and critically revised the manuscript. KJ participated in the management of the patient and drafted the first version of the manuscript. RR performed and interpreted the pathological investigations on the patient materials. TL managed the patient, as well as performing the surgical lung biopsy and critically revised the manuscript.

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