CASE REPORT

Pulmonary actinomycosis and Hodgkin's disease: when FDG-PET may be misleading

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Accepted 31 August 2014

SUMMARY

We present a patient with advanced Hodgkin's disease treated with escalated BEACOPP chemotherapy. The result from the interim fluorodeoxyglucose positron emission tomography with CT (PET-CT) after two cycles of chemotherapy is crucial for treatment guidance for the clinical trial HD18 from the German Hodgkin Study Group. An increase in size and standard uptake value (SUV) of a pulmonary lesion suggesting refractory Hodgkin's disease was documented. Since all other manifestations of the lymphoma responded well to the treatment, the discordant behaviour was suspicious for another reason for this progressive pulmonary lesion. Bronchoscopy revealed Actinomyces species in cultures from bronchial washings. Specific treatment was initiated and consisted of 2 weeks of intravenous penicillin followed by ceftriaxone intravenous for another 4 weeks and subsequent oral amoxicillin to complete 12 months of antibiotic therapy. For the Hodgkin's lymphoma, complete remission was documented after a total of six cycles of escalated BEACOPP.

BACKGROUND

Hodgkin's lymphoma is a common malignant disease that, if treated with a combination of chemotherapy and radiotherapy, has high complete remission rates of 80–90% even if diagnosed as advanced disease.[1] The current standard clinical staging procedures include positron emission tomography with CT (PET-CT) scanning.[2] Furthermore, PET-CT is currently evaluated in large clinical trials (German Hodgkin Trial Group, HD 18, NCT00515554) as a tool for early decision-making.

We present a young patient with Hodgkin's disease whose PET-CT demonstrated improvement in some but progression in other lesions with increased uptake on PET scan after two cycles of dose-intense chemotherapy.

Discordant behaviour of suspected tumour lesions in a highly chemotherapy sensitive disease such as Hodgkin's lymphoma can lead to uncertainty for the patient and the treating physician and should raise suspicion for alternative explanations for PET-positive lesions.

CASE PRESENTATION

A 38-year-old Swiss chimneysweeper with a smoking history of 12 pack years was hospitalised for productive cough over the last 2 months, weight loss of 10 kg during the last 6 months and night sweats. The medical history was completely unremarkable. In a CT scan, mediastinal lymphadenopathy and a pleural effusion on the left side were seen. A PET-CT scan showed increased standard uptake value (SUV) of a mediastinal mass, supraclavicular up to cervical lymph nodes on the left side and pericardial, pleural, diffuse pulmonary (left upper lobe) and bone lesions (figure 1A). Bronchoscopy and biopsy of mediastinal lymph nodes were not conclusive but cytologically showed cells suspicious for malignant disease. Since further differentiation was not possible, Hodgkin's lymphoma, non-Hodgkin's lymphoma and seminoma were included in the differential diagnosis due to localisation and age of the patient.

The final diagnosis was established by a supraclavicular lymph node excision, which revealed a classical nodular-sclerosing Hodgkin's lymphoma. Ann Arbor stage based on symptoms and PET-CT scan was IVBE.

The reason for the productive cough was considered to be a community-acquired pneumonia and the patient was treated empirically with amoxicillin and clavulanic acid because of an elevated C reactive protein and pneumonia-like clinical features, with prompt relieve of these symptoms after 7 days of antibiotic treatment. For the Hodgkin's lymphoma the patient was enrolled in a study-protocol from the German Hodgkin Study Group, HD18 with escalated BEACOPP (NCT00515554). He received two cycles of escalated BEACOPP followed by treatment-evaluation with an interim PET-CT scan.

All the lesions reported on the initial PET-CT showed a good metabolic response apart from the pulmonary infiltration in the apical left upper lobe of the lung, which on the new PET-CT showed progressive SUV and on the CT component had increased in size and density (figure 1B).

INVESTIGATIONS

Primary chemotherapy refractory Hodgkin's disease based on the progressive lung lesion was considered to be very unlikely. Therefore, differential diagnoses included mainly infections, despite a lack of clinically apparent signs of infection. A review of the patient's charts showed a positive culture for *Actinomyces graevenitzii* from the initial bronchoscopy. The culture was initially interpreted as possibly contaminated in the context of diagnosis of a malignant lymphoma and successful treatment of the pulmonary symptoms with a short course of antibiotics. In the light of a progressive lung-lesion on chemotherapy the diagnosis of pulmonary actinomycosis was further investigated with repeat bronchoscopy. The cultures from the bronchial washing revealed *A. graevenitzii* and *A.*

To cite: Weisshaupt C, Hitz F, Albrich WC, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2014-206034

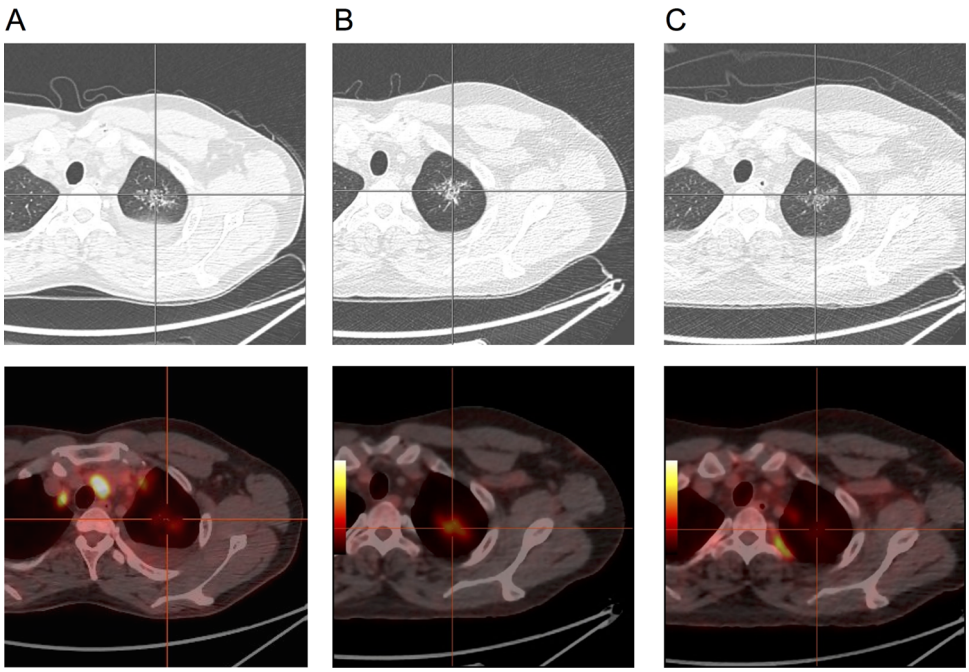

Figure 1 (A) CT and positron emission tomography (PET) before treatment including pathological mediastinal lymph nodes; (B) CT and PET after 2 months of treatment; (C) CT and PET 4 weeks after treatment of the lymphoma and after 3 months of antibiotic treatment of the pulmonary actinomycosis.

odontolyticus, which were both sensitive to penicillin and ceftriaxone. Furthermore, the initial transbronchial biopsy of a paratracheal lymph node grew *Actinomyces* species. Microscopy and culture of bronchial lavage and lymph nodes were negative for other bacteria, mycobacteria and fungi. PCR for *Mycobacterium tuberculosis* was negative from bronchoalveolar lavage and lymph node.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included various causes of lung infections such as tuberculosis, aspergillosis, nocardiosis, actinomycosis or indeed primary refractory Hodgkin's disease of the lung. The patient received prophylactic antibiotic treatment with cotrimoxazole as per protocol of the HD18 trial.

TREATMENT

Initially the patient received penicillin 4 Mio IU intravenously every 4 h for 2 weeks. To allow subsequent outpatient management the antibiotic treatment was switched after 2 weeks to ceftriaxone (2 g intravenously every 24 h) for a total of 4 weeks. A repeat high-resolution CT scan of the chest 6 weeks after initiation of antibiotic treatment showed subtotal regression of the infiltrations in the left upper lobe and treatment was changed to oral amoxicillin (1 g every 8 h) for a total antibiotic treatment duration of 12 months.

The chemotherapy was completed without complications for a total of six cycles of escalated BEACOPP as per HD18 protocol.

OUTCOME AND FOLLOW-UP

The PET-CT scan 4 weeks after completion of six cycles of escalated BEACOPP for stage IV Hodgkin's disease and a total of 3 months of antibiotic treatment for pulmonary actinomycosis showed a complete metabolic response for the lymphoma and almost complete resolution of the infiltration in the left upper lobe of the lung (figure 1C).

DISCUSSION

Pulmonary actinomycosis is a rare infectious disease caused by actinomyces species, mostly by *Actinomyces israelii*, but other pathogenic species have been reported, such as in our case *A. graevenitzii* and *A. odontolyticus*. *Actinomyces* species are microaerophilic or anaerobic Gram-positive rods; histologically, 'sulfur granules' are typically found.[3] Actinomycetes are normal inhabitants of the oral cavity or female genital tract. Growth in sputum or bronchial secretions is considered no proof of active disease, while the diagnosis of (pulmonary) actinomycosis requires growth from a sterile specimen, demonstration of sulfur granules from pus or from a histological specimen. Characteristically, actinomycosis does not respect natural boundaries and can therefore be confused with malignancy. Oral-cervicofacial disease is the most frequent clinical manifestation of actinomycosis. Pulmonary infection accounts for about 15% of all actinomycotic infections.[4] Clinical presentations include history of productive cough, haemoptysis, fever, weight loss and chest pain. Predisposing factors for pulmonary actinomycosis include poor oral hygiene with aspirations and structural underlying lung disease namely a history of tuberculosis or bronchiectasis. Radiological findings are generally unspecific: the most common findings on CT scans are consolidations (74.5%), followed by hilar lymph node enlargement (29.8%), atelectasis (28.7%), cavitation (23.4%) and ground-glass opacity (14.9%).[5]

Our patient, with a concurrent diagnosis of pulmonary actinomcycosis and stage IVBE Hodgkin's disease, had classical symptoms for both diseases. The productive cough and fever were interpreted as non-specific pulmonary infection due to the extensive stage of the Hodgkin's disease with pulmonary, pleural and pericardial infiltration. Despite the smoking history there was no underlying lung disease in our patient and oral and dental hygiene were good.

Our patient had a small consolidation in the left upper lung with a slight FDG-uptake at first presentation. FDG-uptake and

dimensions increased during intensive chemotherapy for Hodgkin's disease, possibly as a result of immunosuppression. A case of a disseminated pulmonary actinomycosis was reported on a patient on infliximab treatment for Crohn's disease,[6] but it remains unclear as to what extent immunocompromised patients have a higher incidence of actinomycosis.[7]

Some type of altered host immunity was probably one of the reasons for the coincidence of lymphoma and actinomycosis, but there is little known about this and our patient was screened prior to initiation of chemotherapy for HIV, hepatitis B and hepatitis C and did not have any known immunocompromising diseases.

Standard treatment for pulmonary actinomycosis consists of high-dose penicillin intravenously for 2–6 weeks followed by oral treatment with oral penicillin V or amoxicillin for a total of 6–12 months. Surgery is an option for complications such as fistulas, empyema or abcesses and in case of treatment refractory or life-threatening haemoptysis.[4]

Hodgkin's disease has an incidence of about 3/100 000 in Western Europe and the USA. The incidence peaks twice, in younger age and for a second time after the age of 60.[8] The current staging assessments include a PET-CT scan, with repeated scans during treatment with prognostic and predictive information.[9] An interim PET-CT after two cycles of chemotherapy shows good predictive information with 3-year progression free survival for PET-positive patients of 28% versus 95% for those with PET-negative scans.[10] This illustrates the importance of accurate interpretation of these interim examinations and the necessity to further investigate discordant or suspicious behaviour of different lesions.

The patient in our case report was treated on a study protocol of the German Hodgkin Study Group, HD18, for advanced cases, with six cycles of escalated BEACOPP and without involved field radiotherapy because of complete metabolic remission in the PET-CT scan after the chemotherapy, this per protocol of the trial.

Treatment naïve Hodgkin's disease is generally chemotherapy sensitive with a treatment failure rate of about 10% for limited disease and up to 10% not reaching complete remission in advanced disease.[11] Differential response, especially on early restaging PET-CT scans, should primarily raise suspicion of alternative reasons for new PET-positive findings.

Patient's perspective

Since the patient has only limited capability of the English language the following statements that the patient gave orally in Swiss German were transcribed:

- I was diagnosed with advanced Hodgkin's disease. I consented to be treated in a clinical trial protocol. As I understood, one of the main decisions of the trial was based on a positron emission tomography (PET) scan after two cycles of chemotherapy (total of four cycles escalated BEACOPP for complete metabolic remission after two cycles or a total of six cycles for patients with non-complete metabolic remission after two cycles of escalated BEACOPP). Naturally, the interim PET-CT scan was very important to me and the possible outcomes based on these results had been well explained to me by my doctors. The fact that most tumour lesions showed a good metabolic response was encouraging, however, the increase in size and uptake of the lung lesion was alarming. The doctors told me that they thought of some kind of infection and that I had to again undergo a bronchoscopy for further investigations. Luckily, chemotherapy continued but the waiting time for the bronchial cultures was difficult. Finally I was told that a rare cause of infection 'Actinomycosis' was found and was considered to be most likely the cause of the growing lung lesion. I learned that this is a treatable infection but that I would have to undergo antibiotic treatment for 1 year.
- Although the time when further tests had to be performed and waiting for the results of the culture caused considerable anxiety not only to me but also to my partner, who is a trained nurse and to my family, I was always well informed of all procedures and of the next steps to come. In hindsight, I am deeply grateful that further investigations had been undertaken.

Learning points

- Pulmonary actinomycosis is often misdiagnosed because it can mimic other infections and is often misinterpreted as malignant formation.
- Diagnosis of actinomycosis is made by anaerobic culture or with the typical histological finding of 'sulfur granules'.
- Treatment of actinomycosis consists of penicillin as the treatment of first choice, first intravenously for about 2–6 weeks, followed by an oral treatment for 6–12 months.
- Fluorodeoxyglucose positron emission tomography positive lesions do not necessarily always reflect malignant disease and in chemotherapy sensitive disease such as Hodgkin's lymphoma a differential response on an early positron emission tomography CT should prompt further investigations for alternative explanations.

Contributors CW wrote the case report, searched the literature and formed the conclusions in the discussion section. FH reviewed the content concerning the lymphoma. WCA reviewed the content concerning the actinomycosis. AO reviewed the whole case and managed the patient. Additional: Joachim Müller helped us with the radiological pictures. All authors contributed to the final draft of the case report.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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