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CLINICAL CASE RECORD

An immunocompromised patient with fever and pulmonary infiltrates

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Abstract
This paper describes the case of a patient with progressive respiratory muscle weakness requiring invasive mechanical ventilation. After extensive work-up he was diagnosed with neurosarcoidosis and treated with immunosuppressive drugs. During the ICU stay he developed new pulmonary consolidations and fever. The differential diagnosis of fever and pulmonary infiltrates in a ventilated, immunocompromised patient is extensive. A systematic and probabilistic approach and close cooperation between the intensive care, infectious diseases, radiology, and pulmonology revealed an uncommon aetiology for this second episode of respiratory failure.

Introduction
The group of immunocompromised patients is heterogeneous and growing in number due to improving treatment opportunities in the Western world. The only thing that connects them is their susceptibility to infection with organisms of low native virulence for immunological normal hosts. The lungs are a known 'weak spot' for both infectious and non-infectious complications such as drug- or disease-related problems, emboli, and idiopathic interstitial lung diseases.[1] Although improving, mortality in immunocompromised mechanically ventilated patients with pulmonary infiltrates remains high, in stem-cell transplant recipients even approaching 90%.[2]
Despite the large amount of literature on this topic many physicians still encounter difficulties in dealing with these patients in daily practice. As an example, we describe our diagnostic challenge in an immunocompromised patient on prolonged mechanical ventilation, with a new episode of fever and pulmonary infiltrates.

We will discuss this patient in the same way as we encounter similar patients in clinical practice. Step by step we will acquire information and as we go, we learn from the contributions and opinions of our colleague consultants.

Case presentation
A 69-year-old male with severe respiratory failure was admitted to the intensive care unit (ICU) of a non-academic hospital for endotracheal intubation and mechanical ventilation. Dyspnoea and orthopnoea had been present for one week and were preceded by several months of progressive peripheral muscle weakness. At admission he exhibited a severe respiratory acidosis with normal oxygenation. The chest X-ray was unremarkable. His past medical history included hypertension and hypercholesterolaemia, for which he was prescribed metoprolol, furosemide and simvastatin. None of his family members were known to have muscle weakness or any other genetic muscle disease.
Despite a thorough evaluation by the neurologist and the rheumatologist, the reason for the muscle weakness remained obscure. Attempts to wean the patient from mechanical ventilation failed due to hypercapnia during weaning trials. He was referred to our hospital for further evaluation and weaning from the ventilator.
After extensive re-evaluation in our centre, a presumptive diagnosis of neurosarcoidosis was established, based on the combination of clinical picture, electromyography, cerebral spinal fluid and inguinal lymph node histology showing granuloma without necrosis; Ziehl-Neelsen stain for tuberculosis was negative. High-dose corticosteroids were administered (methylprednisolone 1000 mg for three days), followed by prednisone (1 mg/kg bodyweight per day). After two months, while still on the ventilator, methotrexate (20 mg once a week) was added to the steroids because of persistent muscle weakness. After three months of immunosuppressive therapy, our patient was still ventilator bound, despite a slight improvement in muscle strength and slow but definite progression in weaning from the ventilator.

At that time he experienced sudden progressive dyspnoea, the next day followed by fever and mild leucocytosis (11.0 x109/l) without elevated C-reactive protein. Sputum production increased but he was not haemodynamically compromised. The chest X-ray revealed atelectasis and new consolidation in the left lower lobe (*figure 1*). Notably, the patient was on selective digestive tract decontamination (SDD) since being admitted to our centre, on cotrimoxazole prophylaxis since on methotrexate and recent surveillance cultures were unremarkable. Piperacillin/tazobactam 4500 mg every eight hours was empirically initiated under the suspicion of a ventilator-associated pneumonia.

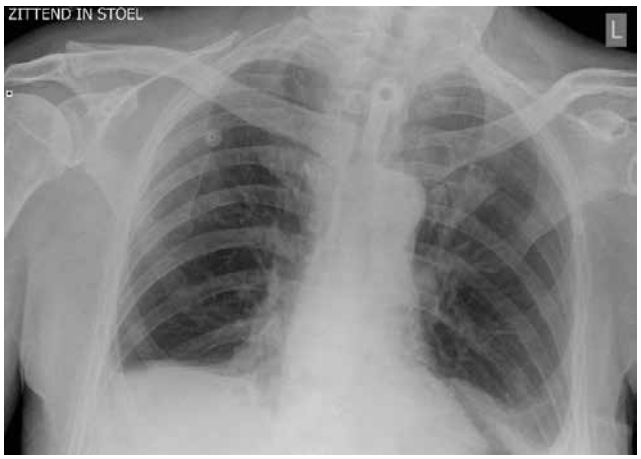

Figure 1. Chest X-Ray showing atelectasis and consolidation in the left lower lobe.

Intensivist:
Fever and consolidations on chest X-ray in an immunocompromised patient on the ventilator has a broad differential diagnosis (*table 1*). An infectious cause is the most likely explanation, in particular when the consolidation is localised, but we should also consider pulmonary complications related to the underlying disease itself or to the initiated drug therapy. Finally, there is always a chance of a more or less unrelated problem such as pulmonary oedema of cardiac origin, pulmonary embolism or malignancy. By using a systematic approach, the chance of missing a treatable cause is reduced.[1,2] In this case we choose to empirically cover hospital-acquired pathogens only, because the patient was stable from a haemodynamic perspective and pulmonary function was not dramatically compromised by the infiltrate. The suspicion of *Pneumocystis* pneumonia (PCP) was low because of the use of PCP prophylaxis, initiated together with methotrexate. However, it might be reasonable to also perform bronchoscopy with bronchoalveolar lavage (BAL) at this stage, in particular in this immunocompromised patient.

Glucocorticoids will dose-dependently increase the risk of infection, due to inhibitory effects on a broad range of T-cell and B-cell responses and depression of phagocytic function

Table 1. Pulmonary infiltrates in an immunocompromised host.[1]

Aetiology	Example
Infectious	Common pathogens or opportunistic or nosocomial infection
Drug-induced	E.g. methotrexate, bleomycin, cyclophosphamide, sirolimus Not related to the primary disease: e.g. amiodarone, nitrofurantoin
Underlying disease	RA, SLE, Goodpasture, Wegener, sarcoidosis, leukemic infiltrate
Haemorrhage	Usually associated with clotting disorders and/or thrombocytopenia
Idiopathic interstitial lung disease	IPF, AIP, NSIP, COP
Other (unrelated to primary disease)	Cardiopulmonary oedema, pulmonary embolus, malignancy, ARDS, TRALI
Combination of the above	

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; IPF = idiopathic pulmonary fibrosis; AIP = acute interstitial pneumonia; NSIP = non-specific interstitial pneumonia; COP = cryptogenic organising pneumonia; ARDS = acute respiratory distress syndrome; TRALI = transfusion related acute lung injury.

of alveolar macrophages and neutrophils. [3] Methotrexate has immunomodulatory rather than immunosuppressive effects on cellular immunity and inflammatory mediators, and is associated with less severe infections than high-dose glucocorticoids. [4] Pulmonary infection is at the top of the differential diagnosis, current literature on this subject points out that early BAL in suspected ventilator-associated pneumonia (VAP) is not improving mortality. [5-7] However, in most studies immunocompromised patients were excluded and in daily practice a BAL is an early consideration in this subgroup.

In addition to the infectious workup I would order a chest computed tomography (CT) scan to rule out pulmonary embolism, given the aspecific presentation and dyspnoea prior to the fever. Besides, in case of abnormalities on imaging, we could direct a possible BAL to the precise lobe. Of note, a CT scan shortly after lavage is undesirable, as lavage will result in transient consolidation and atelectasis, in particular due to loss of surfactant.

Chest CT (*figure 2*) demonstrated a small area with ground-glass opacification in the right upper lobe. Distinct from this area a filling defect was seen in the artery of the left lower lobe, consistent with pulmonary embolism together with atelectasis. Gram staining of the endotracheal aspirate, drawn just before starting piperacillin/tazobactam, revealed a Gram-negative rod, which apparently emerged despite SDD. Colistin nebulisation was initiated as dictated by our SDD protocol, until two surveillance cultures are negative. Culture of the aspirate revealed *Enterobacter cloacae*, susceptible to the antibiotic given. Blood cultures remained sterile, *Aspergillus* or other pathogens were not found in colonisation cultures. In spite of the initiated therapy, in the following days his respiratory symptoms did not improve and the patient remained febrile, but haemodynamically

stable without vasopressors. After five days, the piperacillin/tazobactam was discontinued because of the lack of effect and the desire for further evaluation.

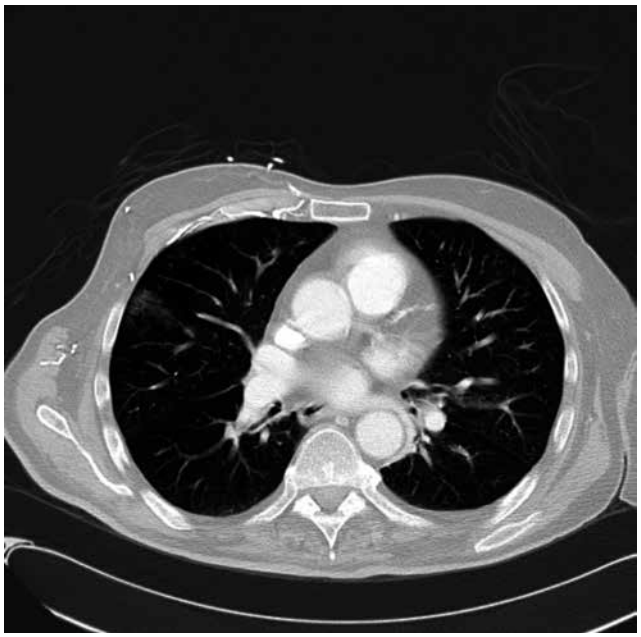

Figure 2. First chest-CT showing a subtle groud-glass opacity in the right upper lobe.

Intensivist:

We are not sure whether the *Enterobacter* found in the endotracheal aspirate is indeed responsible for the current episode of clinical deterioration. This patient is prone to another – potentially opportunistic – infection. It is also not clear to what extent the subsegmental pulmonary embolism is contributing to his clinical condition. Despite controversy over the therapeutic implications of subsegmental pulmonary embolism with unknown clinical significance [8,9] we decided to initiate anticoagulation therapy using a therapeutic dose of fractionated heparin.

By differentiating an acute form (<24 hours) from a more insidious course of the symptoms, and by classifying the abnormalities on chest X-ray and chest CT, we can identify clues leading us to a specific microorganism. Rapid identification of the aetiology avoids potential toxicities of broad-spectrum antimicrobial therapies (most notably nephrotoxicity), drug interactions, and *Clostridium difficile* colitis. On the other hand, it is obviously harmful to delay a correct, targeted therapy, especially in vulnerable patients. For these reasons invasive techniques are often required early in identifying the causative agent or process in the immunocompromised host with pulmonary infiltrates.

In our patient, I would now like to ask the colleagues of the departments of infectious diseases, radiology and pulmonology for their differential diagnosis and advice for the further diagnostic work-up.

Infectious disease specialist:

Bacterial infection is the leading cause of fever and pulmonary infiltrates in a patient on mechanical ventilation.[10] In the era of SDD, the incidence of VAP has significantly decreased, but Gram-negative bacteria are still responsible for the majority of infections.[11] The *Enterobacter* identified is probably of little clinical significance. The presence of intracellular microorganisms and quantitative culture of BAL fluid possibly is more specific than a culture of an endotracheal aspirate.[12]

Multifocal ground-glass opacities can be a sign of viral infection and in this immunocompromised host an infection with a respiratory virus such as influenza or reactivation of, for example, cytomegalovirus, should also be considered. In an immunocompromised host not responding to first-line antibiotics, opportunistic infection caused by mycobacteria, *Nocardia* or fungi should be kept in mind. He has no travel history; he appears to have no specific risk factors for reactivation of tuberculosis and endemic fungi (coccidiodomycosis and histoplasmosis). Also, the CT scan shows no signs of latent tuberculosis infection (calcified nodules, fibrotic scars, pleural thickening, diaphragmatic tenting) and in earlier lymph-node histology Ziehl-Neelsen staining is negative.

Steroid treatment is associated with PCP, caused by the yeast-like fungus *Pneumocystis jirovecii*. In some patients PCP may develop with a prednisone dose of only 16 mg. In addition, in 25% of the patients who are infected with PCP, this develops within eight weeks of immunosuppressive therapy.[13] The suspicion of PCP is low in our patient because we are dealing with a hospital-acquired disease and our patient is on prophylaxis.

Also, invasive aspergillosis is increasingly being recognised as a complication in ICU patients and a recent observational study reported mortality of over 75% among critically ill patients with histologically proven invasive aspergillosis.[14] The prolonged use of corticosteroid therapy puts our patient at risk.[15] It is a difficult diagnosis in the non-neutropenic ICU population; diagnostic criteria (EORTC/MSG) are only validated in haematological and transplant patients and characteristic radiological signs of invasive aspergillosis are usually absent.[16] Aspergillus cultured from endotracheal aspirates is not specific; as with other pathogens it is difficult to discriminate colonisation from invasive disease.[17] In non-neutropenic patients serum galactomannan is not sensitive, but can guide treatment if positive.[17] The gold standard remains histology of pulmonary tissue and this is often hard to get in a mechanically ventilated ICU population. Blot et al. proposed criteria especially adapted to the ICU population; these seem useful particularly due to a high negative predictive value.[16] I would advise a new CT scan to identify new radiological clues, followed by BAL.

Radiologist:

There are several radiographic characteristics of a pulmonary lesion to distinguish: is it a localised consolidation, is there a

more interstitial / peribronchovascular distribution or are there one or multiple nodular lesions? Also, the radiologist will describe the presence of extrapulmonary findings such as pleural effusion or lymphadenopathy.

Quickly emerging consolidations are most likely, but not exclusively, caused by bacteria. A slower progression is more common in fungi, tuberculous or nocardial infections unless a patient is in an immunocompromised state. As mentioned earlier, the halo sign, which is very suggestive of aspergillus infection, is rarely seen in ICU patients.[16] Also, for the emergence of the pathognomic air-crescent sign in the patient, a normal immune response with normal neutrophils is required. In viral infections we expect a more diffuse interstitial pattern, which is – besides fluid overload – also suspicious for PCP or non-infectious causes such as drug-induced lung disease. Multiple nodular lesions give rise to suspicion of *Nocardia* and *Actinomyces* spp., fungi and tuberculosis. In cryptogenic organising pneumonia (COP, historically called bronchiolitis obliterans organising pneumonia or BOOP) the typical pattern is that of multiple patchy opacities, usually peripherally located, but it can also exhibit a focal pattern or diffuse infiltrative opacities.[18] Additional pleural effusion and lymphadenopathy together with a more chronic progression of the disease is suggestive of malignant aetiology. With the imaging in our patient one might think of granulomatosis with polyangiitis, historically called Wegener's granulomatosis. From my point of view the imaging in this patient does not show the typical pattern of sarcoidosis in the lungs.

Pulmonologist:

I agree with the infectious diseases consultant that an infectious origin of the patient's fever and consolidation is most likely. However, the C-reactive protein was low and alternative diagnoses should be considered as well. In fact, pulmonary embolism was found on the CT scan and this could explain his fever. In addition, the differential diagnosis should include other non-infectious causes for inflammation including idiopathic interstitial lung diseases (in particular COP) or drug-induced pulmonary infiltrates. As this patient is known with neurosarcoidosis, pulmonary localisation of sarcoidosis should be considered. However, this seems less likely to develop under steroid and methotrexate treatment and the patient did not demonstrate the typical radiological findings of sarcoidosis in the chest.

When COP is suspected, the definitive diagnosis is based on characteristic findings from lung histopathology (by transbronchial or transthoracic biopsy) and the exclusion of other possible aetiologies.[18] However, given the fact that the response to corticosteroid treatment is unconvincing or insufficient, this diagnosis appears less likely for now.

Methotrexate-induced pulmonary complications can occur in a period of weeks to months after initiation of methotrexate therapy. It is important to recognise this, because discontinuation of methotrexate prevents progression of pneumonitis into fibrosis. Signs and symptoms are nonspecific, including hypoxia and fever, and do not distinguish from pulmonary infection. Other investigations such as BAL and imaging are helpful in identifying or ruling out infection and malignancy but cannot confirm or exclude methotrexate lung. Frequently the clinical response to discontinuation of the methotrexate is the most confirmative of the diagnosis, as a definite diagnostic test is not available.[19] Since high-dose glucocorticoids may be considered as additional treatment, the diagnosis of methotrexate toxicity is less likely in our patient.

The radiologist mentions granulomatosis with polyangiitis but negative anti-neutrophil cytoplasmic (ANCA), anti-nuclear (ANA) and anti-glomerular basement membrane (anti-GBM) antibodies in our patient plus evolvement of the disease during corticosteroid treatment makes an autoimmune process less likely.

In the following weeks, although the ventilator settings and his clinical condition were not worsening, no progression was made in weaning the patient from the ventilator and increased sputum-production persisted. From this moment, the corticosteroids were slowly tapered. Cultures from aspirate obtained by bronchoscopy (without lavage) in order to open an atelectatic left lower lobe revealed no pathogens. A high-resolution CT was performed, several weeks after the initial chest CT. This scan demonstrated progression of the ground-glass appearance in the right upper lobe and it showed that a cavity had developed in this area (*figure 3a*). In addition, a new mass with little mass effect and without cavitation or air-crescent sign had developed (*figure 3b*), together with atelectasis of the middle lobe. Repeated culture from aspirates revealed no pathogens.

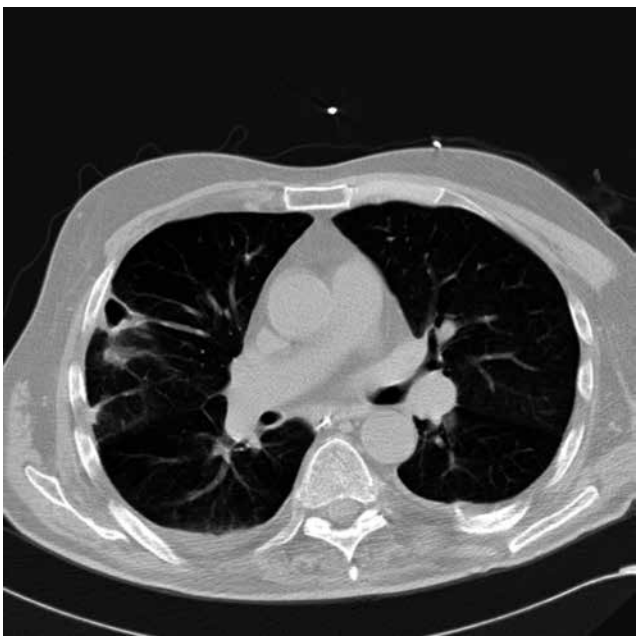

Figure 3a. Repeated chest-CT after a 2 weeks, showing a small cavitary lesion in the right upper lobe.

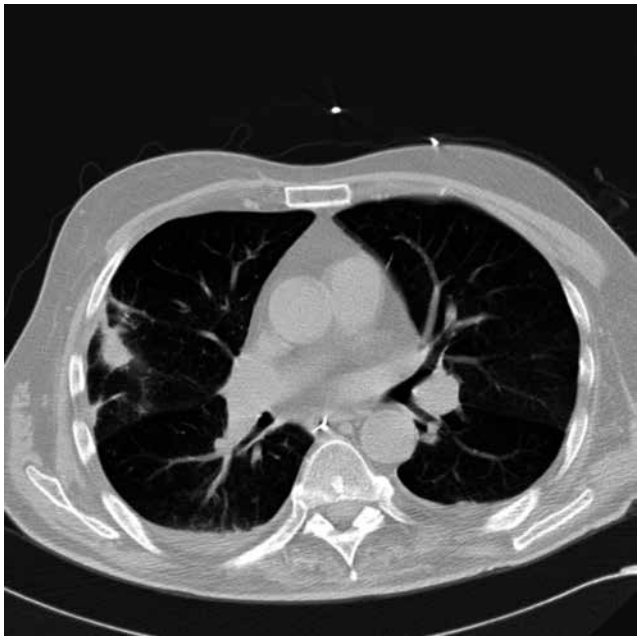

Figure 3b. Same CT showing a new mass without cavitation or air-crescent sign directly besides the cavity.

Radiologist:
The cavitary lesion in the right upper quadrant could be explained by infarction after pulmonary embolism, but the previously found filling defects were only present in the left lung. It also raises the possibility of fungal infection.
The new mass shows no cavitation or air-crescent sign. Alongside hilar and mediastinal lymphadenopathy, sarcoidosis of the lungs could also manifest itself with ground-glass opacification and parenchymal masses or nodular consolidation occasionally with cavitation.[20] However, I think the current images are still not typical for sarcoidosis.
The aspect of the radiological findings may also suggest a malignancy or granulomatosis with polyangiitis but as I understand this does not fit in the clinical picture.

Pulmonologist:
The fact that the patient has already received high-dose corticosteroids for over three months makes the diagnosis of COP, drug-induced lung disease or granulomatosis with polyangiitis very unlikely. Cavitation is an important clue, which narrows our differential diagnosis (*table 2*). Cavitation is consistent with necrosis. The origin of the necrosis can be suppurative (e.g. as in pyogenic lung abscess due to *Klebsiella pneumoniae*), caseous (typically by *Mycobacterium tuberculosis*) or ischaemic (e.g., pulmonary infarction, malignancy). A cavity of any origin is frequently complicated by subsequent superinfection. I agree with the radiologist that a malignant aetiology is less likely, given the rapid development of the cavitation. However, it should be noted that cavitation on a chest CT is found in up to 22% of primary lung cancers.[21] In my opinion, the most obvious primary cause for our patient's problems remains infection. The cavitation, the unilateral abnormalities on imaging, his immunocompromised status and negligible cough strength with high risk of aspiration are consistent with this reasoning. In a recent meta-analysis, open lung biopsy in mechanically ventilated patients with pulmonary infiltrates of unknown origin was associated with a change in therapy in 78% of patients. The lung biopsy provides enough sample for histological analysis and a thorough infectious evaluation. The rate of procedure-related complications was 29%.[22] After CT-guided lung biopsy, chest tube placement or pleurodesis was scarcely necessary.[23]
I would advise a BAL and, if non-conclusive, a CT-guided or open lung biopsy, depending on experience in this centre.

Infectious disease specialist:
In our patient the presence of cavitation suggests a necrotising infection, the cause of which could be fungi, *Nocardia* spp, mycobacteria, *Staphylococcus aureus* and certain Gram-negative bacilli (most commonly *Klebsiella pneumoniae*), or anaerobes.[24] *Aspergillus* has never been cultured in the endotracheal aspirates of our patient, but this is not sensitive enough to rule out invasive aspergillosis. A BAL could be helpful in establishing or excluding these pathogens. Culture requires immediate specimen transport; prolonged anaerobic incubation and specific media can be used to increase the yield of *Nocardia* culture.

Table 2. Differential diagnosis of cavitary lung lesions.[22]

Classification		Examples
Non-infectious	Malignancies	Squamous cell carcinoma, lymphoma, Kaposi's sarcoma
	Rheumatological disease	GPA, sarcoidosis
	Miscellaneous diseases Associated with cavities	Pulmonary infarction, COP, pulmonary Langerhans' cell histiocytosis
Infectious	Common bacterial infections - Necrotising pneumonias and lung abscesses - Septic pulmonary emboli	*Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus milleri*
	Uncommon bacterial infections	*Actinomyces, Nocardia, Melioidosis, Rhodococcus*
	Mycobacterial infections	*Mycobacterium tuberculosis*
		Nontuberculous mycobacteria
	Fungal infections	Aspergillosis, Zygomycosis, Histoplasmosis, Blastomycosis, (Para-) Coccidioidomycosis, *Penicillium, Pneumocystis jirovecii*
	Parasites	Echinococcosis, Paragonimiasis

GPA = granulomatosis with polyangiitis (historically called Wegener's granulomatosis); COP = cryptogenic organising pneumonia.

A BAL was performed the day after the chest CT and showed an active inflammatory process with alveolar macrophages and neutrophils, no fungi or other pathogens were visible on direct microscopy, galactomannan and polymerase chain reactions on BAL were negative. All cultures remained sterile.

After the high-resolution CT, a CT-guided puncture of the cavitating lesion in the right upper lobe was performed. Histology showed a chronically active necrotising inflammation with no clues for specific pathogens. Culture of this material finally provided a breakthrough in the diagnostic work-up: *Gemella* spp. and *Actinomyces odontolyticus* were identified as the presumed pathogens. In addition, a small number of anaerobic Gram-positive cocci and enterococci were cultured, all sensitive to amoxicillin. Ziehl-Neelsen staining was negative.

Infectious disease specialist:
The cavitary lesion in our patient showed multiple micro-organisms, as is often the case in the immunocompromised host. It is a challenge to identify them as fast as possible and to eliminate them with the least possible side effects of too broad antibiotics. *Gemella* spp, *Actinomyces odontolyticus* and anaerobic gram-positive cocci belong to the oral flora and aspiration is central in the pathogenesis of the pulmonary cavitating infection. I think the role of the enterococci is negligible. *Actinomyces odontolyticus* is a Gram-positive facultative anaerobic microorganism belonging to the endogenous flora of the mucous membranes, including the oral cavity. Besides thoracic disease, *Actinomyces* can cause oral-cervicofacial and abdomino-pelvic disease. From the *Actinomyces* spp., *Actinomyces israelii* is responsible for most human infections, but pulmonary infections with *A. odontolyticus* have been described, particularly in immunocompromised patients.[25] Generally the course of the infection is insidious and characterised by non-specific symptoms. *A. odontolyticus* may not be pathogenic on its own, since the current case and some of the previously reported cases have noted concomitant growth of oral flora. *Gemella* spp. is a Gram-positive, facultative anaerobic cocci and resides in the oral cavity and upper respiratory tract. Aspiration of saliva probably leads to the inoculation of – possibly previously damaged – pulmonary parenchyma with *A. odontolyticus*, *Gemella* spp. and anaerobes. *Gemella* spp. are an infrequent cause of infections, and if isolated, *Gemella* is mainly associated with endocarditis,[26] but molecular analysis has shown that *Gemella* spp. are likely to play a role in ventilator-associated pneumonia.[27]

Despite the fact that all isolated organisms are susceptible to penicillin, my advice would be to treat the patient with amoxicillin/clavulanic acid, because the isolation of anaerobes is notoriously difficult and beta-lactamase producing anaerobes may play a causal role as well. The duration of therapy is not clear, but the current recommendation is to treat thoracic actinomycosis with high-dose penicillin for at least two weeks, followed by oral therapy for 6-12 months. Surgery is a therapeutic adjunct only if there are complications, but this should always be combined with prolonged antibiotic therapy.[28]

In our patient amoxicillin/clavulanic acid was started with an intended prolonged duration. The patient's fever subsided and after an ICU stay of 220 days he was finally discharged to a centre where continuous mechanical ventilation was provided. Because of the insufficient effect of the immunosuppressive drugs on muscle strength, these were gradually tapered. A CT scan two months later demonstrated evident improvement of the pulmonary lesions. Given the immunosuppressive state of the patient and the often prolonged treatment needed in actinomycosis, it was decided to continue antibiotics and repeat imaging to determine the duration of therapy.

Commentary

We have discussed a patient with a prolonged ICU stay because of respiratory insufficiency in the context of generalized muscle weakness due to a probable neurosarcoidosis. During prolonged treatment with high-dose corticosteroids and methotrexate, he developed fever and pulmonary consolidations. In our diagnostic work-up we found a cavitating lesion in the right upper lobe. Culture of CT-guided tissue biopsy revealed a mixed flora of *Actinomyces odontolyticus, Gemella* spp. and anaerobes, probably caused by aspiration. Long-term treatment with amoxicillin/clavulanic acid led to clinical improvement.

Immunosuppressive drugs are being increasingly used, for instance in patients with bone marrow or solid organ transplant, but also in patients with autoimmune diseases. Pulmonary infection remains the most common type of tissue-invasive infection in the immunocompromised host, therefore intensivists, pulmonologists, specialists in infectious diseases and radiologists should join forces to determine the cause as soon as possible and to initiate the appropriate therapy.

Our patient is an excellent example demonstrating that a probabilistic approach to clinical decision-making can be helpful. One can find clues in the timeframe and characteristics in imaging. When an infection is suspected, one should consider less common microorganisms after excluding the more frequently found pathogens. Sometimes clues can be found in the history of the patient, e.g. travel and occupation, prior surveillance cultures and use of antibiotics, comorbidity (e.g. mucor in diabetics) and type of immune deficit.

This case again supports the statement that reliable material for microscopic evaluation and culture is extremely valuable in immunocompromised patients with pulmonary infiltrates of unknown aetiology. We should strongly consider early and invasive diagnostic techniques including BAL, CT-guided lung biopsy or open lung biopsy. If postponed, it may delay appropriate therapy.
In our case the patient was not unstable from a haemodynamic

perspective, neither did he show severe respiratory compromise, but he did not progress in weaning from the ventilator. This resulted in a rather slow diagnostic work-up. In retrospect, the diagnosis could have been made earlier and potentially the duration of his ICU admission could have been reduced.

Disclosures

All authors declare that they have no conflict of interest.

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