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Case report

Disseminated *Mycobacterium avium* complex infection in a woman with anti-interferon-γ autoantibodies

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ABSTRACT

Defects in the interleukin-12/interferon-gamma (IFN-γ) pathway and anti-IFN-γ antibodies have been associated with severe nontuberculous mycobacteria (NTM) infections. Consequently, disseminated NTM infections should prompt investigations for immunodeficiency. Herein, we report a case of a treatment refractory and ultimately disseminated and fatal *Mycobacterium avium* complex infection in a 71-year-old woman of Thai origin. Simultaneously, she had recurrent *Salmonella kentucky* cultured from stool samples and chronic perianal HSV-2 lesions. Late in the course of disease, anti–IFN-γ autoantibodies were demonstrated. Clinical studies investigating immunomodulating therapy and treatment among patients with anti-IFN-γ autoantibodies are lacking and, in this case, treatment seemed of a more palliative nature.

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Introduction

Mycobacterium avium complex (MAC) is a group of nontuberculous mycobacteria usually causing disease in individuals with immunodeficiency or structural lung disease [1]. Defects in the interleukin-12 (IL-12)/interferon-gamma (IFN-γ) pathway and autoantibodies against IFN-γ have been associated with severe NTM infections [2–5] and Salmonella infections and Herpesviridae reactivations have also been associated with these immunodeficiencies [2–5].

Herein, we report a case of treatment refractory, disseminated and ultimately fatal MAC infection. Anti-IFN-γ antibodies was the most likely cause of the disseminated MAC infection, as well as recurrent *Salmonella kentucky* and persisting herpes simplex virus (HSV)-2 skin lesions.

Case

A 71-year-old female, originally from Thailand, presented with fatigue, weight loss (8–10 kg), 3–4 daily loose stools, night sweats, and recurring fever. She had a medical history of diabetes mellitus (type 2), hypertension, dyslipidaemia, and paroxysmal atrial fibrillation and was a never smoker. The patient had lived in Denmark for 23 years, and during a recent 3-year stay in Thailand, she was diagnosed with tuberculosis and treated only for a shorter period for unknown reasons. In March 2017, initial physical examination revealed a pale, cachectic woman with universal lymphadenopathy. Computed-tomography (CT) scan showed a small, apical cavity in the right lung as well as small noduli and a discrete infiltrate in the left lower lobe. A cervical lymph node biopsy showed lymphoglandular bodies with multiple mature lymphocytes, but no sign of granulomas. An HIV test result was negative.

Microscopy of sputum was positive for acid fast bacilli and antituberculosis treatment was initiated. However, MAC (unnamed subspecies) was subsequently cultured (Fig. 1) and the treatment was changed to a standard MAC regimen with rifampicin, ethambutol and clarithromycin. Four months later, the treatment was

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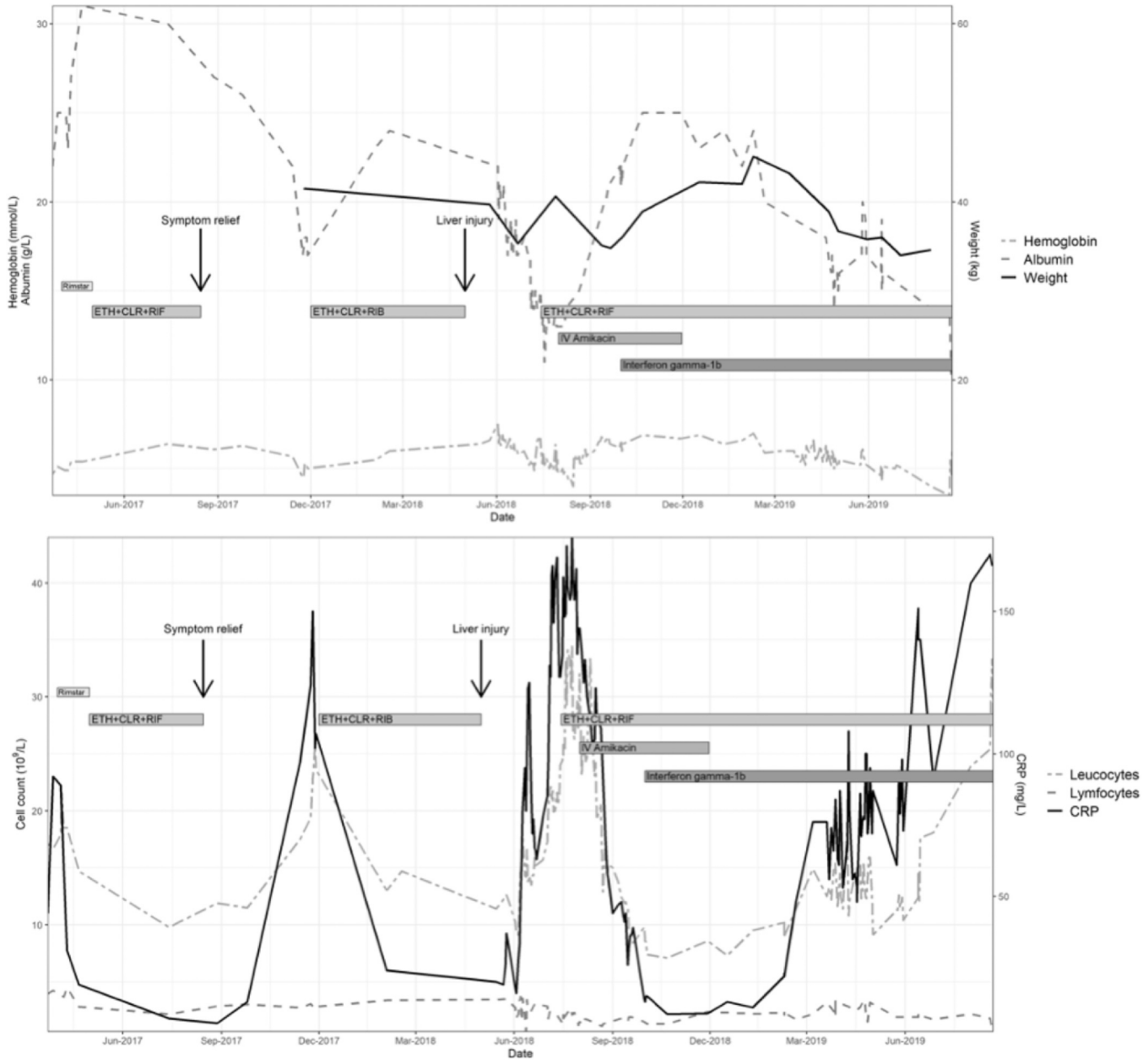

Fig. 1. Overview of hemoglobin, albumin and weight (upper figure) and leukocytes, lymphocytes and C-reactive protein (lower figure) during nontuberculous mycobacterial treatment throughout the entire course of disease. Abbreviations: ETH, ethambutol. CLR, clarithromycin. RIF, rifampicin. RIB, rifabutin. CRP, C-reactive protein.

discontinued due to lack of pulmonary symptoms. In November 2017, a positron emission tomography–computed tomography (PET/CT) scan showed progression of infiltrates including a new infiltrate in the left upper lobe as well as enhancement in multiple lymph nodes below and above the diaphragm. Endobronchial ultrasound-guided bronchoscopy revealed fibrotic-looking tissue and MAC was again cultured from sputum and still susceptible to macrolides. Thus, MAC treatment was reinitiated. Rifampicin was replaced by with rifabutin due to in vitro drug resistance. However, five months later, the treatment was paused for one and a half months because of elevated liver enzymes (alkaline phosphatase 1080 U/L (reference 35–105)) and ALAT 198 U/L (reference [10–45]). Imaging of the liver showed hepatomegaly and fibrosis as well as irregularity of the bile ducts suggesting primary biliary cirrhosis. Moreover, anti-mitochondrial antibodies were measured, but due to the clinical status of the patient, a liver biopsy was never performed. The suspicion of primary biliary cirrhosis was never confirmed.

In June 2018, admission of the patient was warranted due to severe diarrhea with dehydration and continuous weight loss. Treatment was paused for a couple of weeks. Eventually, oral administration of clarithromycin was changed to intravenous for ten days and parenteral nutrition was initiated, which improved the clinical status significantly. The patient continued with oral MAC treatment and four months of intravenous amikacin.

Immunological examination showed severely reduced concentration of CD4 T-cells 0.26 × 109/L (Table 1). CD8 T-cell count was within normal range, but the distribution of CD8 T-cell subsets were distributed toward terminal differentiation 47% (defined as CD57pos) and HLA-DR expression was upregulated on both CD4 and CD8 T-cells (51% and 81% expressed HLA-DR) indicating immune activation. The fraction of CD4 recent thymic emigrants (CD45ROneg CD4RApos CD31pos) was normal but the overall concentration was low presumably secondary to the reduced total CD4 T-cell concentration. IgA, IgE and IgG and classes were all significantly

Table 1
Overview of immunological analyses.

	Results	Reference values	Unit
Leukocytes	12.4	4.5–10	10^9/L
Lymphocytes	1.8	0.7–4.8	10^9/L
B cells, $CD19^+$	0.18	0.09–0.57	10^9/L
T cells, $CD3^+$	0.59	0.69–2.70	10^9/L
$CD4^+$ T-cells	0.26	0.39–1.70	10^9/L
$CD8^+$ T-cells	0.30	0.19–1.03	10^9/L
Ratio CD4/CD8	1.1		
RTE of CD4 T-cells	7.0	6.4–51.0[a]	%
RTE	0.025	0.042–0.823[a]	10^9/L
NK cells, $CD16/56^+$	0.50	0.08–0.56	10^9/L
Immunoglobulins			
IgA	653–1412	70–430	mg/dL
IgG	2537–2874	610–1490	mg/dL
IgG1	1730	280–800	mg/dL
IgG2	516	120–570	mg/dL
IgG3	156	24–125	mg/dL
IgG4	486	5.2–125	mg/dL
IgM	80–99	39–208	mg/dL
IgE	1286–1480	0–150	kU/L
Somatic hypermutation of expressed immunoglobulin kappa light chain genes	76	27–88	% of mutation fraction
Complement system			
Classical activation	164	> 69%	% of positive control
Lectin activation	175	> 1%	% of positive control
Alternative activation	164	> 30%	% of positive control
Lymphocyte stimulation			
Pokeweed Mitogen	67	–	% of positive control
Anti-CD3/CD28/CD2 stimulation	94	–	% of positive control
IFN-γ /IL-12 axis function[b]			
	Stimuli	**LPS**	**LPS+IFN-γ**
TNF-α (pg/mL)	Control 1	158	994
	Control 2	269	1893
	Patient	31	190
IL-12p70 (pg/mL)	Control 1	288	1734
	Control 2	434	2357
	Patient	229	247
	Stimuli	**PHA**	**PHA+IL-12**
IFN-γ (pg/mL)	Control 1	748	5323
	Control 2	956	5660
	Patient	undetectable	undetectable

Abbreviations: CD, cluster of differentiation. RTE, recent thymic emigrants. NK, natural killer. Ig, immunoglobulin. IFN, interferon. IL, interleukin. TNF, tumor necrosis factor.
[a] RTE reference values: http://www.mayomedicallaboratories.com/test-catalog.
[b] Luminex kit used for measuring Cytokine production: ProcartaPlex Mulitplex Immunoassey, ThermoFisher.

increased. Whole-genome sequencing of an immunodeficiency panel did not reveal mutations associated with the patient's condition. Functionally analyses of the IFN-γ/IL12 axis including measurement of TNF-α and IL-12 production following IFN-γ boosted LPS in vitro stimulation and IFN-γ production following IL-12 boosted phorbol myristate acetate stimulation was reduced in relation to both TNF-α and IL-12 production although not absent. In addition, IFN-γ production was undetectable upon stimulation. Thus, reduced TNF-α and IL-12 production in the functional investigation the IFN-γ/IL-12 signaling pathway gave evidence of dysfunction in this pathway comparable to findings like in patients with molecular defects described to cause Mendelian Susceptibility to Mycobacterial Diseases (MSMD) [6]. The undetectable IFN-γ production was initially interpreted as possibly secondary to severe CD4 T cell lymphopenia. However, when screening for autoantibodies (GM-CSF, IFNα, IFN-γ, IL-10, IL-1α and IL-6) severely elevated levels of presumably neutralizing IL-1α- and IFN-γ-autoantibodies were detected [7]. Subsequently, interferon gamma-1b 60 µg subcutaneous thrice weekly was commenced.

Both clinical and paraclinical parameters continued to improve after treatment intensification. Likewise, a PET/CT showed significant regression of all infiltrates in thorax. However, after eight months of clinical improvement, the patient presented with lower back pain with radiation to the lower extremities and clinical signs of infection. MRI and PET/CT of columna were unable to exclude spondylodiscitis, but a percutaneous biopsy from the left pedicle of L5 including culture (including mycobacterial), 16S/18S PCR and pathology did not establish a diagnosis. Meanwhile, *Candida lusitania* was found in blood cultures, and in July 2019, a biopsy from a swollen lymph node was positive for acid fast bacilli. Once again, HRCT showed progression in infiltrates (Fig. 2). The treatment was subsequently changed to palliative care after twenty-nine months of active treatment and the patient died two weeks later.

During the entire course of disease, the patient suffered from severe chronic perianal HSV-2 skin lesions. The chronic diarrhea was examined with intestinal biopsies, which showed lymphocyte and plasma cell infiltration, but celiac antibodies were not detected. *Salmonella kentucky,* was cultured from feces twice. Though, the cultures were made a year a part, the patient might have contracted the bacteria in Thailand. Also, MAC was cultured twice in the blood. In addition, several different skin lesions were sporadically occurring. Histological examination of an erythema nodosum looking lesion was identified as leukocytoclastic vasculitis and another skin lesion contained granulomatous inflammation and giant cells.

Discussion

We describe a case of a treatment refractory and ultimately disseminated and fatal MAC infection in a 71-year-old woman of Thai origin. Simultaneously, she had recurrent *Salmonella kentucky* cultured from stool samples and chronic perianal HSV-2 lesions. Late in the course of disease, anti-IFN-γ autoantibodies were demonstrated.

Typically, MAC infections are considered either a local pulmonary infection in patients with structural lung damage, or a disseminated opportunistic infection associated with HIV or other immunodeficiencies [1]. Consequently, immunodeficiency should always be investigated in disseminated infections. In this case, the patient was suspected of a localized pulmonary infection for a long period, while an immunodeficiency due to anti–IFN-γ autoantibodies was found relatively late in the course of disease. The QuantiFERON®-TB was indeterminate, as it has been reported for several cases [3], and it has been suggested that the autoantibodies neutralize IFN-γ secreted from the lymphocytes. Consequently, an indeterminate QuantiFERON®-TB test result due to undetectable or extremely low levels of IFN-γ support the diagnosis of anti–IFN-γ autoantibodies [8].

Since the beginning of the millennium, several cases of disseminated infections with NTM in the presence of high titers of anti-IFN-γ autoantibodies have been described among HIV-negative patients [5,9–12]. The prevalence of this immunodeficiency, defined 'anti-IFN-γ autoantibody-associated immunodeficiency syndrome', is unknown and is probably underdiagnosed [2,4]. The syndrome is most often reported among midlife females of East Asian heritage [2,5]. Yet, the patient was somewhat older in this case. The mechanisms and triggers of the disease are not clearly understood [4], but the syndrome has been associated with HLA-DRB1 and HLA-DQB1 [13–15]. Moreover, molecular mimicry has been proposed as a

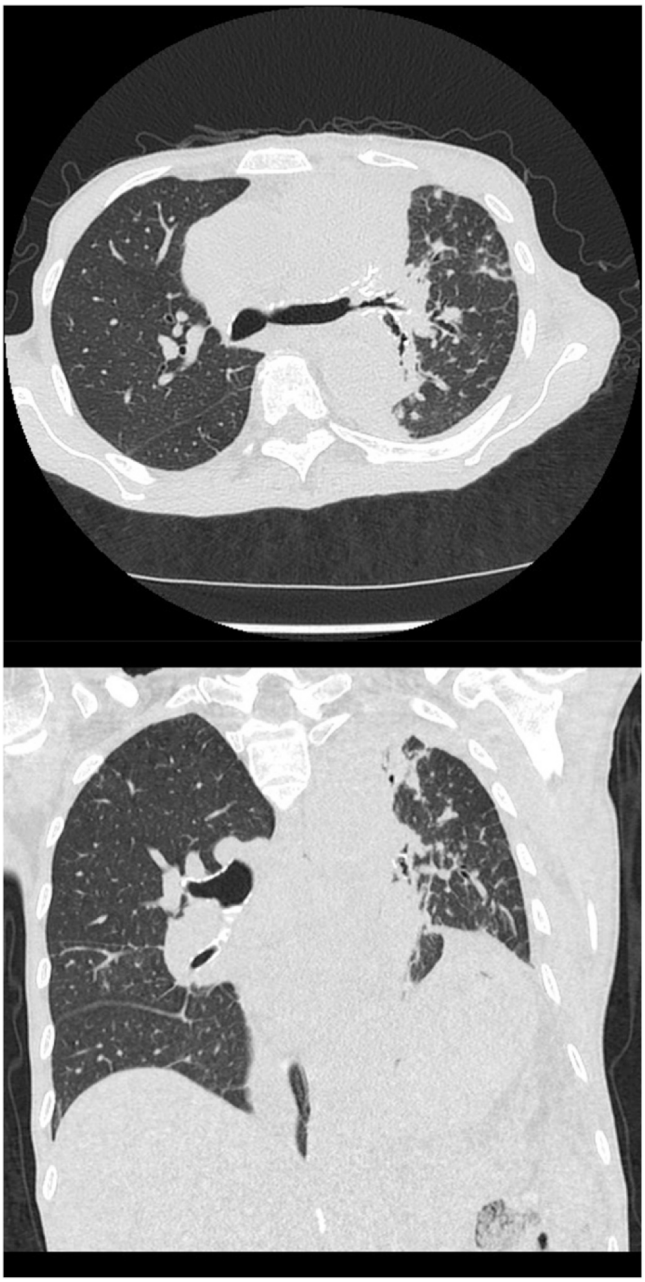

Fig. 2. High-resolution computed tomography of the lungs of the patient in August 2019. The scan showed continued consolidation of the left upper lobe and endobronchial obstruction of the airways on the left side suggestive of mucus or polyps. In addition, the scan showed increasing consolidation of the left lower lobe, diffusely scattered infiltrates in the left lung and unchanged smaller left-sided pleural effusion.

potential mechanism of autoantibody production [16]. Prior to disease onset, most of the patients are immunocompetent [12].

The patient in our case presented with classical symptoms, such as weight loss, fever, reactive cutaneous lesions, and generalized lymphadenopathy [3]. In addition, the patient presented with Herpes and Salmonella infections as previously described in patients with IFN-γ autoantibodies [2,3,5] and in patients with inborn defects in the IL-12/IFN-γ pathway, the so-called 'Mendelian susceptibility to mycobacterial disease', i.e., impaired IFN-γ receptors, downstream signaling or production of IFN-γ [17]. Tuberculosis as well as more rare infections as *Talaromyces marneffei* among patients with anti-IFN-γ autoantibodies have been described in several reports although more infrequently than NTM [2,5,18]. These opportunistic infections are most likely secondary to the immunodeficiency.

Moreover, we observed that the patient had a low CD4 T-cell count, and elevated levels of IgA and IgE as well as anti-IL-1α, anti-actin and anti-mitochondrial antibodies, which to our knowledge has not been described as a common finding in this syndrome. In addition, involvement of the liver and intestines was prominent. Whether this was due to antibiotic toxicity or live infiltration with MAC and subsequent immune reconstitution inflammatory syndrome rather than primary biliary cirrhosis remains speculative.

The patient was treated for a very long period and was for shorter periods in clinical improvement. During initial treatment, antibiotics were discontinued after only four months, suggesting that many clinicians are unaware that treatment is recommend for at least one year after culture-conversion. As a matter of fact, the disease seemed to progress with dissemination of MAC outside the lungs. At the moment, the evidence about treatment of patients with anti-IFN-γ antibodies remains sparse and cure is rarely achieved [2,4]. Antimicrobial therapy is most often insufficient with slow remission or frequent relapses [19]. Adjunctive treatment with rituximab, IFN-γ, intravenous immunoglobulin, corticosteroids, cyclophosphamide, and plasmapheresis have been tried [2,3]. In hindsight, the patient may not have benefitted from the IFN-γ therapy due to inactivation by the autoantibodies although this strategy has previously been suggested in the management of patients with anti-IFN-γ autoantibodies [20]. Yet, we do not know the exact epitope for the autoantibodies and the binding capacity. Unfortunately, we did not fully understand the clinical presentation until late in the course of disease. Rituximab is the most studied immunomodulatory drug among patients with anti-IFN-γ autoantibody-associated immunodeficiency syndrome, and was considered during the course of disease, but was withheld, awaiting effect of antibiotics. Although evidence is still needed, rituximab appears to improve clinical outcomes by decreasing both titers and neutralizing capacity of the antibodies [2–4]. However, it is still unclear what the preferable drugs are and what the optimal strategy is, e.g., supporting the immune system and/or on inhibiting the synthesis of autoantibodies. Evidence about the ideal treatment including dosing and duration and the clinical implications of reducing anti-IFN-γ antibodies titers is needed.

In conclusion, disseminated NTM infections should always prompt investigations for immunodeficiency including examination of the IL-12/IFN-γ pathway. Interestingly, this case had several other immunological abnormalities besides anti-IFN-γ autoantibodies. Clinical management of patients with NTM and anti-IFN-γ autoantibodies is exceptionally challenging, as there is little evidence to support the treatment, and we recommend that the patients are managed at specialized clinics.

Author statement

VND wrote the first draft and did literature research with major inputs from BUN. The conception and design of the case report was conducted by VND, BUN and ABA. All authors critically revised the article for important intellectual content. The patient was treated by ABA. All authors approve of the final version of the article.

Conflicts of interest

None to declare.

Consent

Informed consent was given from the next of kin.

Ethical approval

In our setting, ethical approval for case reports are not required if informed consent is given.

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