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Case Report

The hidden hypothesis: A disseminated tuberculosis case

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ABSTRACT

Case presentation: 77-year-old former smoker admitted because of fatigue and abdominal distention. Past medical history positive for two previous hospitalizations for pericardial and pleural effusions (no diagnosis achieved). At admission erythrocyte sedimentation rate was 122 mm per hour. Baseline investigations revealed ascitic, pleural and pericardial effusion. Effusions were tapped: neoplastic cells and acid-fast bacilli (AFB) were not identified, aerobic and mycobacterial culture resulted negative. QuantiFERON TB-Gold test was negative. Total body PET-CT and autoimmunity panel were negative. A neoplastic process was considered the most likely explanation. Before signing off the patient to comfort care, a reassessment was performed and an exposure to tuberculosis during childhood was documented. Because of constrictive pericarditis, pericardiectomy was performed: histologic examination showed chronic pericardial inflammation without granulomas, but Ziehl-Neelsen stain identified AFB and PCR was positive for *Mycobacterium tuberculosis* complex. Patient was started on anti-TB therapy with resolution of the effusions in the following months. Genes associated with defects in innate immunity were sequences and dentritic cells were studied, but no alterations were identified.
Discussion: A Bayesian approach to clinical decision making should be recommended. Interpretation of diagnostic tests should take into account the imperfect diagnostic performance of the majority of these tests. Further studies to investigate genetic susceptibility to tuberculosis are needed.

Case presentation

A 77-year-old Caucasian man presented on 4 January 2016 with fatigue and abdominal distention for 4 weeks. He did not report fever, chills, night sweats, weight loss, hyperchromic urine, or acholic feces. The patient was a former smoker and alcohol abuser. Past medical history was positive for arterial hypertension, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney injury, and hypothyroidism. Six year before admission, a bronchoscopy was performed to evaluate a lesion in the apical area of the right lung (Figure 1): bronchoalveolar lavage fluid cytology and mycobacterial culture were negative. In the last four years before admission the patient was hospitalized twice because of recurrent pleural, peritoneal, and pericardial effusions: a final diagnosis was never achieved. Current medications included: amiodarone, transdermal nitroglycerin, furosemide, canrenone, levotiroxin, erythropoietin, and pantoprazole. On physical examination the patient appeared anasarcatic with a temperature of 36.4 °C, a blood pressure of 136/87 mmHg, a heart rate of 84 beats per min, and a peripheral oxygen saturation rate of 96%. Body max index was 23.8 (height 175 cm and weight 73.0 kg). Heart sounds were irregular, neither murmurs nor rubs were noted. Jugular venous distention was present. When lung auscultation was performed, breath sounds were absent in the right lower lung field; crackles were

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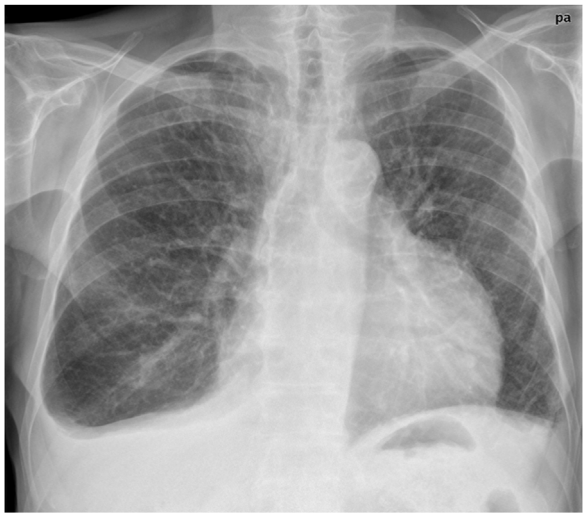

Figure 1. Chest radiograph.

reported in the left lower lung field. The abdomen was distended due to ascites; liver and spleen were not palpable. Laboratory tests revealed: white blood cell 5340 per mmc, hemoglobin 9.4 g/dl, platelets 161,000 per mmc, creatinine 4.0 mg/dl, urea 169 mg/dl, sodium 131 mEq/l, clorum 95 mEq/l, potassium 5.8 mEq/l, aspartate aminotransferase 13 U/l, alanine aminotransferase 6 U/l, total bilirubin 0.4 mg/dl, alcalin phosphatase 69 U/l, total proteins 7.2 g/dl, albumin 3.9 g/dl, gamma globulins 1.9 g/dl, and erythrocyte sedimentation rate 122 mm per hour. A chest and abdomen CT documented bilateral pleural effusions, pericardial effusion, and peritoneal effusion. Liver and spleen morphology and size was within normal limits. A paracentesis was performed and 3000 ml of transudate were removed (see Table 1). QuantiFERON-TB Gold test (Qiagen, Germantown, MD, US), HIV test, and autoimmunity markers (antinuclear antibodies, anti-smooth muscle antibodies, and anti-neutrophil cytoplasmic antibodies) were negative. The patient was started on diuretics and a partial resolution of the effusions was achieved. The patient was discharge home.

After few months of well-being, the patient presented on 9 July 2016 complaining of fatigue and dyspnea. Pleural, pericardial, and peritoneal effusions were documented at admission. A positron emission tomography and a new chest and abdomen CT scan were performed, but no significant findings were identified. Due to the lack of an etiologic diagnosis, the persistence of the effusions, and the patient's medical history, a neoplastic process was considered the most likely explanation. However, before signing off the patient for comfort care, a final in-deep assessment was performed and an exposure to tuberculosis during childhood was documented. Two paracentesis and a thoracentesis were performed, draining a total of 10,8 l of peritoneal fluid and 1,6 liters of pleural fluid, respectively. Trans-thoracic echocardiography highlighted an ubiquitous pericardial effusion (20 mm) which was conditioning a paradoxical movement of the interventricular septum (Figure 2). As a consequence, a two pericardiocentesis were performed using a subxiphoid approach and approximately 250 ml of bloody pericardial effusion were drained each time. Since invasive right and left cardiac catheterization was consistent with constrictive pericarditis, the patient underwent a pericardiectomy on 25 August 2016. Pericardiectomy is the gold-standard treatment of constrictive pericarditis. Pericardial samples were sent for histology and hematoxylin and eosin stain revealed features of chronic inflammation. Despite the absence of granulomas, Ziehl-Neelsen staining was performed and acid-fast bacilli were identified. Furthermore, *Mycobacterium tuberculosis* DNA was identified in the pericardial samples (PCR). Pericardial fluid cultures did not grow *M. tuberculosis.* On 29 August 2016 patient was started on anti-TB therapy (isoniazid 300 mg q24h, pyrazinamide 1500 mg 3 times a week, rifampin 600 mg q24h, ethambutol 1200 mg 3 times a week; anti-TB medications dosage was adjusted to renal function) and on prednisone (50 mg q24h). Few days later the patient was discharged home.

After discharge, significant fluctuations in the patient's renal function were recorded. Pyrazinamide and ethambutol were discontinued approximately 8 weeks after they were started,

Table 1
Microbiology and pathology investigations performed in the period 2016–2017.

Sample	Date	Volume (l)	Proteins (g/dl)	Glucose (mg/dl)	White blood cells (cell/mmc)	Gram stain	Bacterial aerobic culture	Acid fast bacilli stain	Mycobacterial culture	*Mycobacterium tuberculosis* DNA	Pathology
Peritoneal effusion	04/01/16	3.5	2.9	109	180 (granulocytes and lymphocytes)	Negative	Negative	NP	NP	NP	Negative
Peritoneal effusion	13/07/16	5.6	3.9	109	120 (granulocytes and lymphocytes)	NP	NP	NP	NP	NP	Negative
Peritoneal effusion	19/07/16	5.3	NP	NP	NP	Negative	Negative	Negative	Negative	Negative	Negative
Pleural effusion	20/07/16	1.6	4.3	92	NP	Negative	Negative	Negative	Negative	NP	Negative
Pericardial effusion	21/07/16	1.6	5.2	27	NP	Negative	Negative	Negative	Negative	NP	Negative
Pericardial effusion	18/08/16	0.2	2.9	24	NP	Negative	Negative	Negative	Negative	NP	Negative
Pericardial effusion	25/08/16	NP	NP	NP	NP	Negative	Negative	Negative	Negative	NP	Negative
Pericardium	25/08/16	NP	NP	NP	NP	NP	NP	Positive	NP	Positive	Chronic inflammation, no granulomas
Peritoneal effusion	29/11/16	3.6	NP	NP	NP	Negative	Negative	Negative	Negative	Negative	Negative
Pleural effusion	30/11/17	0.5	3.9	87	NP	Negative	Negative	Negative	Negative	Negative	Negative

NP: not performed.

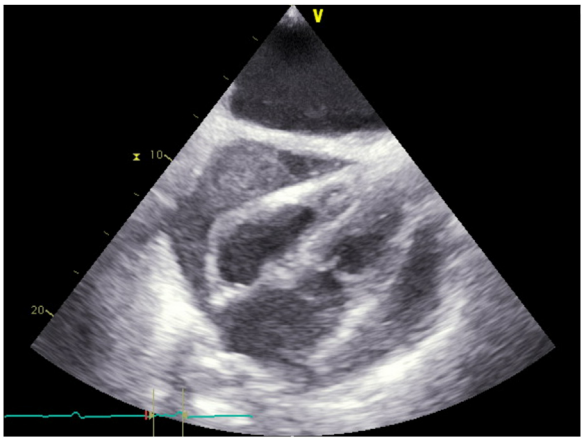

Figure 2. Trans-thoracic echocardiography showing an ubiquitous pericardial effusion.

while prednisone was tapered and isoniazid and rifampin were continued. Unfortunately, a recrudescence of pleural and peritoneal effusions was documented by the end of November 2016 and the patient was re-hospitalized. Prednisone was discontinued and a five-drug anti-TB regimen was prescribed (rifampin 600 mg q24h, isoniazid 300 mg q24h, ethambutol 1200 mg q24h, pyrazinamide 1500 mg q24h, and moxifloxacin 400 mg q24h). Ethambutol, pyrazinamide, and moxifloxacin were discontinued on 2 July 2018, while rifampin and isoniazid were discontinued on 15 January 2019. Since then, the patient has been experiencing a good quality of life without any relapse of symptoms.

The persistent negativity of QuantiFERON-TB Gold test and the absence of granulomas in the pericardial samples analyzed prompted us to search for immune defects associated with an increased susceptibility to *M. tuberculosis*. Genes associated with defects in IFN-gamma response genes (CYBB, GATA2, IFNG, INFGR1, IFNGR2, IKBKG, IRF8, ISG15, IL12RB1, STAT1, IL12B, TYK2) or other innate immunity defects (ARPC1A, ARPC1B, CARD9, CARD11, CEBPE, CLEC7A, IL17A, IL17 F, IL17RA, IL17RC, IRAK4, MBL2, MPO, MyD88, RAC2, ROCC, STAT2, STAT4, TIRAP, TLR2, TLR3, TLR4, TLR9, TRAF3IP2/ACT1, TRAF3, TRIF, UNC93B1I, and WDR1) were sequenced (Next Generation Sequencing, Ion Torrent, ThermoFisher Scientific, US), but no alterations were identified. Similarly, dentritic cells (DC) were studied: plasmacytoid DC (BDCA2 +CD123+CD4+) and myeloid DC (CD1c+CD4+CD19−CD14−) represented 0.30% (normal range: 0.16–0.76%) and 0.76% (normal range: 0.18–0.92%), respectively, of the total peripheral blood mononuclear cells.

Discussion

This case raises several important points regarding disseminated tuberculosis. First, our case suggests that initial diagnostic hypotheses should be progressively updated with objective new information, as proposed by Bayes's rule (McGrayne, 2012). Specifically, while an evidence-based approach would have discarded the hypothesis of disseminated tuberculosis due to initial lack of microbiological evidences, a Bayesian approach allowed us to reassess the probability of disseminated tuberculosis based on newly available epidemiological information (previous exposure to tuberculosis) and prompted us to second level histology investigations that finally confirmed the presence of tuberculosis. As Feynman well said, 'it is scientific only to say what is more likely and what less likely, and not to be proving all the time the possible and impossible. And we always try to guess the most likely explanation, keeping in the back of the mind the fact that if it does not work we must discuss the other possibilities. How can we guess what to keep and what to throwaway? Sometimes that means that we have to throwaway some idea; at least in the past it has always turned out that some deeply held idea had to be thrown away' (Feynman, 1965).

Second, diagnostic tests for detecting *M. tuberculosis* into effusions are characterized by imperfect sensitivity and specificity and their suboptimal diagnostic accuracy should be taken into account in the clinical reasoning-process. The sensitivity of AFB smear, mycobacterial culture, and *M. tuberculosis* PCR on pleural fluid are <10%, 25%, and 20–90%, respectively (Gopi et al., 2007). Also, the sensitivity of pleural tissue culture and pleural tissue histology are suboptimal: 39–80% and 50–97%, respectively (Berger and Mejia, 1973; Diedrich et al., 2016). At this regard, the Bayesian PERCH model could serve as an example to account for the limited diagnostic performance of microbiology tests when attempting an etiologic diagnosis in the setting of infectious diseases (Knoll et al., 2017; O'Brien et al., 2017).

Finally, TB pathogenesis is complex and far from being understood: this case emphasizes the limited knowledge we have of an old disease (Bellamy et al., 2000; Kampmann et al., 2005; Mitsos et al., 2003; Pan et al., 2005; Tosh et al., 2006). Despite extensive immunology investigations we were not able to identify the mechanisms determining the negative result of QuantiFERON-TB and the absence of granulomas on histology in our patient (Pai et al., 2008). While alcohol consumption and immunosenesce may have predisposed this patient to the development of tuberculosis, we are left wondering which immune mechanisms allowed the escape of *M. tuberculosis* in our patient.

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