



## Case Report

## The hidden hypothesis: A disseminated tuberculosis case

Sergio Foresti<sup>a</sup>, Maria Rita Perego<sup>b</sup>, Manuela Carugati<sup>c,d,\*</sup>, Anna Casati<sup>e</sup>,  
Cristina Malafronte<sup>e</sup>, Marco Manzoni<sup>f</sup>, Raffaele Badolato<sup>g</sup>, Andrea Gori<sup>c,h</sup>, Felice Achilli<sup>e</sup>

<sup>a</sup> Division of Infectious Diseases, Ospedale San Gerardo ASST Monza, Via Pergolesi 33, Monza, Italy

<sup>b</sup> Division of Internal Medicine, Ospedale San Gerardo ASST Monza, Via Pergolesi 33, Monza, Italy

<sup>c</sup> Division of Infectious Diseases, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, Milan, Italy

<sup>d</sup> Division of Infectious Diseases, Duke University, 300 Trent Drive, Durham, USA

<sup>e</sup> Division of Cardiology, Ospedale San Gerardo ASST Monza, Via Pergolesi 33, Monza, Italy

<sup>f</sup> Department of Medicine and Surgery, Pathology Section, University of Milano-Bicocca, Milan, Italy

<sup>g</sup> Division of Paediatrics, Università degli Studi di Brescia, P.le Ospedali Civili di Brescia 1, Brescia, Italy

<sup>h</sup> Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Festa del Perdono 7, Milan, Italy



## ARTICLE INFO

## Article history:

Received 8 April 2019

Received in revised form 13 May 2019

Accepted 20 May 2019

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

## Keywords:

Tuberculosis

Diagnostic performance

Bayes

## 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 sequenced and dendritic 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.

© 2019 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 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 anasarclitic 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

\* Corresponding author at: Division of Infectious Diseases, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, Milan, Italy.

E-mail addresses: [s.foresti@asst-monza.it](mailto:s.foresti@asst-monza.it) (S. Foresti), [mr.perego@asst-monza.it](mailto:mr.perego@asst-monza.it) (M.R. Perego), [manuela.carugati@policlinico.mi.it](mailto:manuela.carugati@policlinico.mi.it) (M. Carugati), [a.casati@asst-monza.it](mailto:a.casati@asst-monza.it) (A. Casati), [c.malafronte@asst-monza.it](mailto:c.malafronte@asst-monza.it) (C. Malafronte), [marco.manzoni@unimi.it](mailto:marco.manzoni@unimi.it) (M. Manzoni), [raffaele.badolato@unibs.it](mailto:raffaele.badolato@unibs.it) (R. Badolato), [andrea.gori@unimi.it](mailto:andrea.gori@unimi.it) (A. Gori), [f.achilli@asst-monza.it](mailto:f.achilli@asst-monza.it) (F. Achilli).

<https://doi.org/10.1016/j.ijid.2019.05.023>

1201-9712/© 2019 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

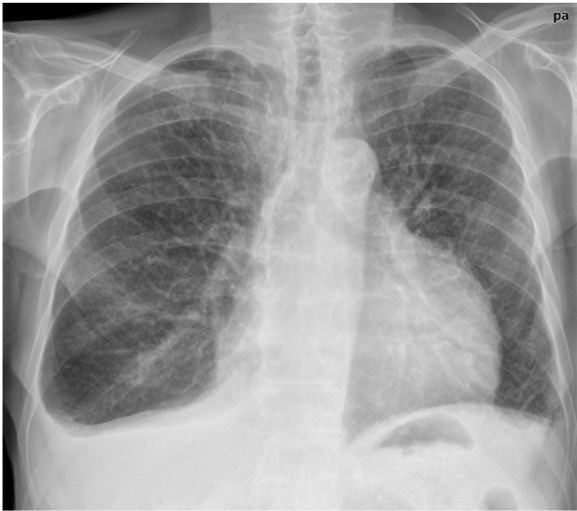


Figure 1. Chest radiograph.

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.

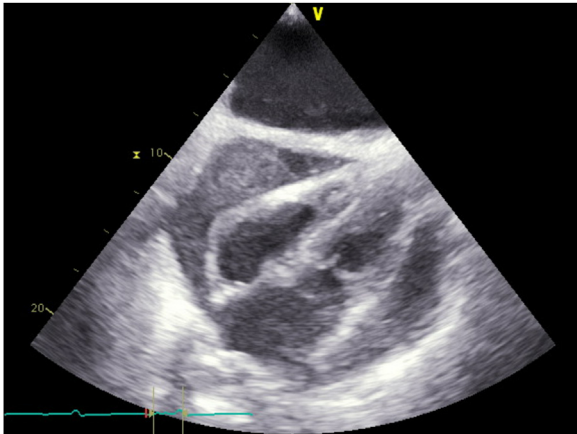
After few months of well-being, the patient presented on 9 July 2016 complaining of fatigue and dyspnea. Pleural, pericardial, and peritoneal effusions were documented at admission. A positron emission tomography and a new chest and abdomen CT scan were performed, but no significant findings were identified. 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 10,81 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 | <i>Mycobacterium tuberculosis</i> 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<br>Negative |
| 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, INFR1, IFNGR2, IKBKG, IRF8, ISG15, IL12RB1, STAT1, IL12B, TYK2) or other innate immunity defects (ARPC1A, ARPC1B, CARD9, CARD11, CEBPE, CLEC7A, IL17A, IL17F, IL17RA, IL17RC, IRAK4, MBL2, MPO, MyD88, RAC2, ROCC, STAT2, STAT4, TIRAP, TLR2, TLR3, TLR4, TLR9, TRAF3IP2/ACT1, TRAF3, TRIF, UNC93B1, and WDR1) were sequenced (Next Generation Sequencing, Ion Torrent, ThermoFisher Scientific, US), but no alterations were identified. Similarly, dendritic 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 immunosenescence 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.

## Funding sources, conflict of interest, and ethical approval

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors do not have any competing interest to declare. Due to the case report nature of the manuscript, no ethical approval was required.

## Acknowledgements

We thank our patient, our colleagues, and our research support staff.

## References

- Bellamy R, Beyers N, McAdam KP, Ruwende C, Gie R, Samaai P, Bester D, Meyer M, Corrah T, Collin M, Camidge DR, Wilkinson D, Hoal-Van Helden E, Whittle HC, Amos W, van Helden P, Hill AV. Genetic susceptibility to tuberculosis in Africans: a genome-wide scan. *Proc Natl Acad Sci USA* 2000;97:8005.
- Berger HW, Mejia E. Tuberculous pleurisy. *Chest* 1973;63:88–92.
- Diedrich CR, O'Hern J, Wilkinson RJ. HIV-1 and the *Mycobacterium tuberculosis* granuloma: a systematic review and meta-analysis. *Tuberculosis* 2016;98:62e76.
- Feynman R. The character of physical law. 12th ed. Cambridge: MIT Press; 1965.
- Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. *Chest* 2007;131:880.
- Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, Nicol M, Schölvinck E, Relman D, Waddell S, Langford P, Sheehan B, Semple L, Wilkinson KA, Wilkinson RJ, Riss S, Hibberd M, Levin M. Acquired predisposition to mycobacterial diseases due to autoantibodies to IFN- $\gamma$ . *J Clin Invest* 2005;115:2480.
- Knoll MD, Fu W, Shi Q, Prospero C, Wu Z, Hammitt LL, Feikin DR, Baggett HC, Howie SRC, Scott JAG, Murdoch DR, Madhi SA, Thea DM, Brooks WA, Kotloff K, Li M, Park DE, Lin W, Levine OS, O'Brien KL, Zeger SL. Bayesian estimation of pneumonia etiology: epidemiologic considerations and applications to the pneumonia etiology research for child health study. *Clin Infect Dis* 2017;64: S213–27.
- McGrayne SB. The theory that would not die. 1st ed. New Haven: Yale University Press; 2012.
- Mitsos LM, Cardon LR, Ryan L, et al. Susceptibility to tuberculosis: a locus on mouse chromosome 19 (Trl-4) regulates *Mycobacterium tuberculosis* replication in the lungs. *Proc Natl Acad Sci USA* 2003;100:6610.

- O'Brien KL, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Howie SRC, Knoll MD, Kotloff KL, Levine OS, Madhi SA, Murdoch DR, Scott JAG, Thea DM, Zeger SL. Introduction to the epidemiologic considerations, analytic methods, and foundational results from the pneumonia etiology research for child health study. *Clin Infect Dis* 2017;64:S179–84.
- Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177.
- Pan H, Yan BS, Rojas M, et al. Ipr1 gene mediates innate immunity to tuberculosis. *Nature* 2005;434:767.
- Tosh K, Campbell SJ, Fielding K, et al. Variants in the SP110 gene are associated with genetic susceptibility to tuberculosis in West Africa. *Proc Natl Acad Sci USA* 2006;103:10364.