Metastatic cancer masquerading as miliary tuberculosis in an immunocompetent young adult

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SUMMARY

A healthy, immunocompetent South Asian man in his mid-20s, with a medical history of gastric ulcer, presented to Accident & Emergency with pleuritic chest pain, shortness of breath, fever, night sweats, weight loss, dry cough and asymptomatic iron deficiency anaemia. Following his initial assessment and investigations (chest X-ray, CT and blood tests), a diagnosis of miliary tuberculosis (TB) was made and empirical antimicrobial treatment started. However, subsequent microbiological testing, including urine, blood, induced sputum and lymph node sampling, was negative. Being interpreted as non-diagnostic, the antimicrobial therapy was continued. Following a clinical deterioration while on treatment, the patient's case was re-evaluated and further investigations, including a repeat CT and a liver biopsy, confirmed a diagnosis of stage IV (T1aN3bM1) gastric carcinoma. Our case highlights the diagnostic challenges in differentiating metastatic cancer from miliary TB. We also focus on possible cognitive biases that may have influenced the initial management decisions.

BACKGROUND

Cancer is rare in adolescents and young adults (AYAs), defined here as anyone aged between 15 and 39 years old. Yet, in industrialised countries, it is still one of the most common causes of death in this age group, behind only homicides, suicides and unintentional injury (accidents).[1] Moreover, it is recognised that AYAs with a variety of cancers will have a poorer prognosis when compared with both children and older adults and that cancer diagnoses are more likely to be delayed.[2–8] The latter is likely to be due to a variety of reasons but an understandably low suspicion of cancer by both patient and clinician is thought to be a major cause.[9 10]

The following case highlights the diagnostic challenges associated with metastatic cancer in AYAs, specifically the difficulty in differentiating its presentation from miliary tuberculosis (TB) and the cognitive biases that can affect clinicians when managing such difficult cases.[11]

CASE PRESENTATION

A previously fit and well South Asian man in his mid-20s presented to Accident & Emergency (A&E) with a 4-day history of pleuritic chest pain at the onset of the COVID-19 pandemic in the UK. In addition, he reported fever, dry cough, shortness of breath on exertion (particularly one flight of stairs), 2 days of night sweats and a 4 kg weight loss over 1 month. He had returned to the UK from the Czech Republic approximately 2 weeks prior and presented to another A&E 1 week before, where he was discharged with the likely diagnosis of COVID-19 infection.

The patient denied any other travel history or unwell contact and was stated as heterosexual. His only medical history was a *Helicobacter pylori*-negative bleeding gastric ulcer, which was diagnosed 2 months earlier while in the Czech Republic for which he required two units of blood transfusion. He was not certain if any sample was taken and sent for histology during the endoscopy. He completed proton-pump inhibitor treatment 2 weeks ago and was not taking any medications on admission. There was no known family history (including cancer) or hereditary disease.

On examination, his vital signs were: respiratory rate of 16; oxygen saturation of 96% on air; heart rate of 87 beats per minute; blood pressure of 117/75 mm Hg and temperature of 36.6°C. On general inspection, he appeared slim with moist mucous membranes and a BCG scar was noted on his deltoid. He had no palpable lymphadenopathy. His lung sounds were described as 'harsh' bilaterally. Other general examinations were unremarkable.

INVESTIGATIONS

At admission, his C reactive protein (CRP) was raised at the level of 139 mg/L, despite a normal white cell count of 9.6×10^9/L. His COVID-19 PCR swab was negative, while his chest X-ray (CXR), as illustrated in figure 1, showed a left-sided pleural effusion with bilateral reticular shadowing supporting a possible diagnosis of miliary TB. Meanwhile, his haemoglobin level returned to be 92 g/L with a mean cell volume of 71 fL/cell, iron level of 2.9 µmol/L and transferrin of 5%, characterising iron deficiency anaemia. Considering his history of gastric ulcer requiring blood transfusion, the medical team started him on iron-replacement therapy and consulted the gastroenterology team, who advised an interval outpatient oesophagogastroduodenoscopy (OGD) given his haemodynamically stable clinical status.

Consistent with this working diagnosis, his contrast-enhanced CT scan of the chest demonstrated interlobular septal thickening and bilateral effusions (figure 2). An indeterminate 1 cm hypoattenuating lesion in segment 8 of the partly imaged liver was also identified and reported as 'may be related to suspected diagnosis of TB but cannot be characterised further'. As he also reported headache and blurry vision during his first A&E admission the week before, an MRI of the brain was requested and did not show any features suggestive

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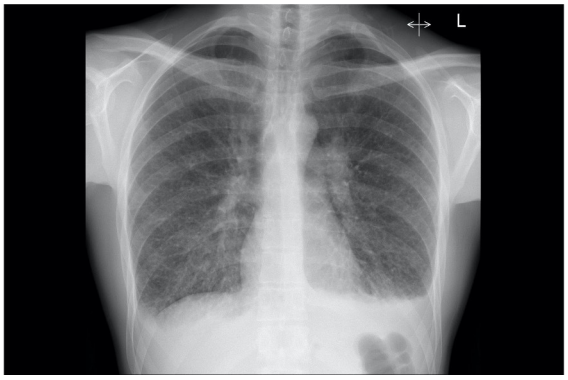

Figure 1 Chest X-ray on admission. It showed reticulonodular shadowing throughout both lung fields, bilateral blunting of costophrenic margins and a small left-sided pleural effusion.

of granulomatous disease. Following that, three urine acid-fast bacilli samples and one induced sputum sample were collected but all corresponding GeneXpert, molecular test, smear and culture for *Mycobacterium tuberculosis* (MTB) yielded either negative results or no growth. Similarly, the respiratory panel, covering influenza A, influenza B, respiratory syncytial virus, rhinovirus/enterovirus RNA, parainfluenza RNA, adenovirus DNA, human metapneumovirus RNA, *Bordetella* DNA, *Bordetella pertussis* DNA and *Mycoplasma pneumoniae* DNA, did not detect any other cause of infection. He was also HIV, hepatitis B and C negative.

The patient was cared for by the infectious disease team with clinical opinions offered by respiratory medicine. As the pleural effusion was small and the pleura not thickened on CT, it was decided to perform an endoscopic bronchial ultrasound with fine-needle aspiration from an enlarged station 7 thoracic lymph node for histology and microbiology. The needle aspirate revealed lymphocytes and histiocytes with no signs of granuloma, caseous necrosis or malignant cells. The molecular test for MTB and the Ziehl-Neelsen stain on smear again came back negative. Although a transbronchial biopsy was planned, the procedure was terminated early due to hypoxia and no sample was obtained. A further attempt was suggested but the patient did not consent due to concerns about the risk of pneumothorax with the procedure.

An interferon-release assay test was not performed in accordance with trust guidance, as this test is reserved locally for the

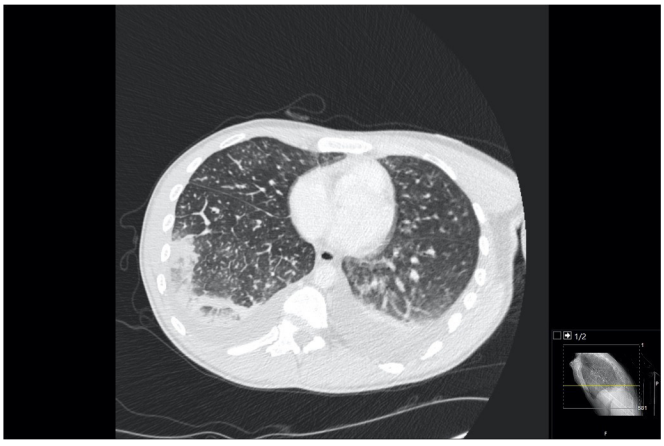

Figure 2 CT scan of the thorax. This transverse slide illustrated the interlobular septal thickening and bilateral effusion.

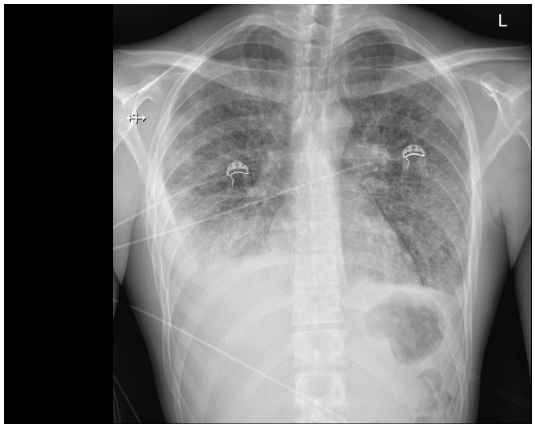

Figure 3 Chest X-ray on second admission. It identified worsening right effusion, widespread nodular shadowing and bilateral hilar lymphadenopathy.

detection of latent TB. Rather, and despite the initial negative cumulative diagnostic investigations for miliary TB, the patient was started on an empirical standard anti-TB treatment regime of Rifinah 300 mg/150 mg, Ethambutol 800 mg and Pyrazinamide 2 g (RIPE). He remained afebrile for 48 hours and was discharged 4 days post-treatment with a downtrending CRP and oxygen saturation of 94% on room air.

DIFFERENTIAL DIAGNOSIS

Three days later, the patient was readmitted to the same hospital due to worsening breathlessness. He had a low-grade fever of 37.9°C and oxygen saturation of 85% on room air. His white cell count and CRP had risen from 10.2×10^9/L and 109 mg/L on discharge to 14.6×10^9/L and 144 mg/L, respectively. A repeat CXR, as shown in figure 3, identified worsening right effusion, widespread nodular shadowing and bilateral hilar lymphadenopathy. As he was recently started on anti-TB treatment, this presentation was presumed to be secondary to the TB-immune reconstitution inflammatory syndrome (TB-IRIS). However, the possibility of metastatic cancer being a differential diagnosis was also communicated to the family. Of note, the patient reported new nausea and occasional vomiting since starting the RIPE, which was attributed to an adverse effect.

Four days into the second admission, the patient developed new pleuritic chest pain and a CT pulmonary angiogram was performed. It ruled out pulmonary embolism but detected enlargement of right hepatic lobar low attenuation foci and new multifocal vertebrae lucencies in comparison with the previous CT. Following this, a CT of the abdomen and pelvis was performed, which demonstrated para-aortic and mesenteric node enlargement.

The patient also underwent an MRI of his spine, which revealed high T2-enhancing lesions in every vertebral body as well as the rib, sternum and pelvis, sparing only the distal sacrum and coccyx. These findings were concluded to be in keeping with hepatic abscess formation, extrapulmonary nodal involvement and spondylodiscitis/osteomyelitis caused by miliary TB. Malignancy was reported as a less probable differential diagnosis given the brisk interval deterioration on imaging. However, the consultant clinician in charge of the patient's case was sufficiently concerned about the apparent clinical deterioration despite RIPE and the lack of any confirmatory microbiology, that they requested a further biopsy attempt. As such, interventional radiology-guided liver biopsy was performed and sent for

histology, microscopy, culture and sensitivity as well as molecular test for MTB. While awaiting the biopsy result, the patient lost his sensation in sacrum and penis, developed urinary retention and desaturated to 79% on room air, resulting in his transfer to the high dependency unit. The biopsy returned a week later demonstrating metastatic adenocarcinoma suspicious of primary gastrointestinal origin. An urgent OGD was performed for gastric biopsy, which established the diagnosis of a metastatic gastric signet-ring cell carcinoma. All other TB-specific investigations remained unremarkable and his anti-TB treatment was ceased, with improvements in his nausea.

TREATMENT

The patient spent 4 days on the high dependency unit before being stepped down to the ward for symptom management. A do not attempt resuscitate decision was put in place with the consent of the patient. He was deemed unsuitable for surgery by the neurosurgery and orthopaedics teams. The acute oncology team also ruled out the option of palliative radiotherapy as he was unable to lie flat for the intervention and his performance status precluded the use of any systemic chemotherapy. The patient remained under the clinical care of the oncologists and the palliative care teams for end-of-life care and symptom control. He also received constant support from the physiotherapists and dietitians to assist with his activities of daily living and poor intake with low body mass index, respectively. He struggled psychologically, and was understandably very frustrated, angry and low following the diagnosis and learning of the expected short prognosis. He expressed a desire for his family and friends to visit regularly. However, as this occurred very early on during the COVID-19 pandemic, the hospital trust was only allowing up to two close family members to visit at a time. During this period, he consented to genetic screening for his family.

OUTCOME AND FOLLOW-UP

The patient deteriorated rapidly with worsening pain and respiratory failure. He eventually passed away peacefully 11 days after the diagnosis.

DISCUSSION

Uncertainties in diagnosing and treating miliary TB

John Jacob Manget coined the term miliary TB in 1700.[12] It was derived from the Latin word *miliarus*, to describe the tiny tubercles resembling millet seeds in size and appearance. Miliary TB is potentially fatal and results from lymphohematogenous dissemination of the MTB bacilli. It accounts for less than 2% of all TB cases in young, immunocompetent adults, but responsible for more than 20% of all extrapulmonary TB cases overall.[13–19] The multiple clinical manifestations, ambiguous radiological findings and difficulty in isolating TB continue to pose diagnostic and therapeutic challenges even today.[20] It proves to be even more elusive in the AYA demographic as the disease tends to be paucibacillary in nature (lower bacillary load) and the diagnostic yield varies according to sampling technique and anatomy.[20 21] For example, positive smear and culture results can vary from methods largely, ranging from 46.8% detection within bronchoscopic fluid to 88.9% and 90.9% from liver and lymph node biopsies, respectively (figure 4). Miliary TB is fatal without treatment and has a mortality rate of as high as 25%–30% in adults despite anti-TB treatment. As such, clinicians are often understandably reluctant to delay the start of treatment, even in the face of diagnostic uncertainties.[22–31]

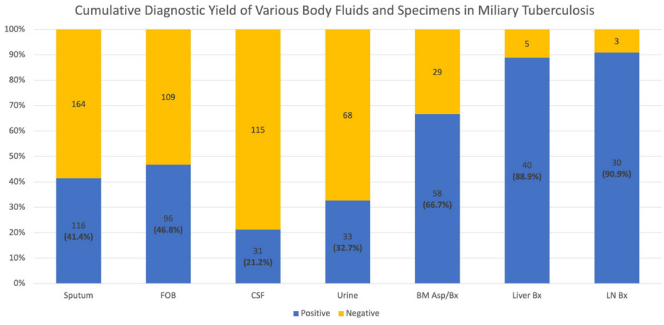

Figure 4 Cumulative diagnostic yield of various body fluids and specimens in the diagnosis of miliary tuberculosis. While the yield cannot be comparable across series due to the lack of standards in criteria employed across studies, it can be used appropriately in an individual patient to establish the diagnosis of miliary TB. Adapted from Sharma *et al*.[20] BM Asp, bone marrow aspirate; Bx, biopsy; CSF, cerebrospinal fluid; FOB, fibreoptic bronchoscopy; LN, lymph node.

Another challenge faced in this case was the uncertainty in determining the therapeutic response of the anti-TB treatment in its early stage. This patient was discharged with clinically stable observations and improving inflammatory markers following 4 days of RIPE but readmitted 3 days later with a low-grade fever of 37.9°C, oxygen saturation of 85% on room air, worsening dyspnoea and uptrending inflammatory markers, raising the possibility of TB-IRIS. This paradoxical worsening of symptoms and/or advancement in radiological findings has been reported in an estimated 2%–23% of immunocompetent, HIV-negative patients during or after the completion of anti-TB treatment, and also frequently raises the possibility of a treatment lag time, misdiagnosis or multidrug-resistant TB, which were all also considered in our patient.[32–38] Such ambiguity complicates the clinical management and frequently amplifies patient and family anxiety. Indeed, this patient struggled to understand why further tests were required after starting TB treatment. It is worth noting that the median time for TB-IRIS onset in HIV-negative patients has been estimated to be between 21 and 56 days after treatment initiation.[37] As such, it is less probable in this specific case.

Miliary TB, metastasis and our cognitive bias in AYAs

Miliary TB can be challenging to differentiate from metastatic cancer, as both can present with similar multisystem symptoms and signs, many of which are not specific to either cancer or a chronic infection, for example, progressive muscle wasting, weight loss, night sweats and fever.[39] Furthermore, initial radiological investigations, although typically abnormal, may not be able to differentiate between the two possibilities. In hindsight, we analysed several different forms of cognitive bias that might have influenced decision-making in this specific case of a young, immunocompetent adult and summarised them in table 1. First, the presenting symptoms and signs (ie, pleuritic chest pain, fever, weight loss, dyspnoea) may have been subconsciously paired to an infectious aetiology, on account of the patient's young age, ethnicity (South Asian) and originating country (Czech Republic). This could have occurred due to a base rate bias (otherwise known as base rate fallacy or neglect). This is a form of cognitive bias, whereby individuals overlook the underlying incidence rates of conditions or population-based knowledge in favour of individuating information.[40] In fact, if one compares the incidence of TB in the Czech Republic and UK between 2000 and 2018, it is clear that the Czech Republic has had a consistently lower TB incidence since 2004[41] (figure 5).

Table 1 Summary of different types of cognitive bias encountered in this clinical scenario

Type of bias	Description
Base rate bias	This occurs in clinical practice when the underlying incidence of conditions or population-based knowledge, related to ethnicity, nationality, age, gender and other factors, is neglected.[40]
Anchoring bias	This occurs when clinicians are unable to adjust diagnostic probabilities as new conflicting information surfaces.[42]
Confirmation bias	This occurs when clinicians selectively choose information gained that fits their preconceived diagnosis, instead of analysing them fairly.[40]
Specialty bias	This occurs when clinicians prioritise differential diagnoses within their specialty due to confinement by their domain knowledge.[43]
Diagnostic momentum	This occurs when clinicians continue a clinical course initiated by prior clinicians without independently assessing all information available.[40]

Second, cognitive bias could also have manifested as an anchoring bias, confirmation bias, specialty bias and diagnostic momentum.[40 42–44] A known clinician fallibility is the tendency to anchor to their initial impressions, despite new or conflicting information arising to suggest an alternative diagnosis. In other words, the clinical information that suited the original working diagnosis is more likely to be subconsciously cemented and used to support the clinician's belief, while other conflicting information is dismissed as either atypical, inaccurate, otherwise explained or interpreted in such a way as to still confirm the original beliefs.[42] An example of bias arising from this case was the omission of an early endoscopy. This case was discussed postmortem in a senior consultant-led forum and much greater emphasis was placed on obtaining an early endoscopy, which would have ultimately led to a prompter correct diagnosis. However, it had been originally felt by gastroenterology that a gastric ulcer had already been confirmed, that a diagnosis of miliary TB was already made and that an endoscopy was not indicated acutely as the patient was haemodynamically stable. However, it was not questioned why this young patient would have acquired a non-malignant *H. pylori*-negative gastric ulcer with no pre-identified risk factors such as excessive non-steroidal anti-inflammatory drug use.

In this case, the patient was first under the care of the infectious disease team, from which he was investigated extensively for infective differential diagnoses, before he was transferred to be under the care of the respiratory team for the continuation of care of presumed miliary TB. We explore how specialty bias, which described how years of experience and habit could make experts put more emphasis on diagnosis within their domain, due to their natural utilisation of forward diagnostic reasoning mode, may have influenced clinician decision-making behind the investigations suggested.[43] Together with premature diagnostic labelling or pigeonholing, these biases can often set off a momentum, as management will often not be thoroughly re-evaluated by subsequent independent clinicians.[40 45] Although there was no objective way to determine if clinical judgement was affected by such bias, there was evidence of open-mindedness by the patient's respiratory consultant that ultimately leads to further investigation and a diagnosis of metastatic gastric cancer being made. This allowed the patient to discontinue the antimicrobial treatments (that were causing adverse effects) and the medical team to focus on optimum palliative care support to minimise symptoms during the terminal phase of the illness, rather than continuing to pursue futile active treatment.

We encourage clinicians to minimise base rate bias, anchoring bias, confirmation bias, specialty bias and diagnostic momentum by remaining open-minded, acknowledging uncertainty, continually re-evaluating (including others' assessments), seeking others' opinions and by regularly reflecting on difficult cases. It is also vital to practise metacognition, that is, begin to develop an insight into one's own thoughts including an understanding of the patterns behind them.[40 42 46 47]

Figure 5 A line graph comparing the tuberculosis incidence rate per 100 000 people in the Czech Republic and the UK between 2000 and 2018. It showed a consistently lower incidence in the former since 2004. Its incidence is also 48% lower than that of the UK in 2018 comparatively (5.4 vs 8.0 per 100 000 people). Adapted from the Global Tuberculosis Report, by the WHO.[41]

Learning points

- The diagnosis of miliary tuberculosis can be challenging and the condition difficult to differentiate from metastatic cancer in adolescents and young adults. It is vital for the medical team to consider the latter early.
- As clinicians, we should keep an open mind, develop metacognition and seek others' help to minimise cognitive bias wherever possible to avoid pitfalls in the investigation and management of our patients.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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