Persistent Fevers in a Returning Traveller despite Malarial Treatment. Malarial Antigen positive but no parasites seen. Is there an alternative diagnosis?

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INTRODUCTION

With international travel increasing[1], naturally there will be an increased number of travelers that will develop a febrile illness.
The differential diagnosis is often broad and a positive test result that seems to be consistent with the patients symptoms is very helpful.
However, if symptoms persist despite adequate treatment, the diagnosis may need re-evaluation as described in this case.

CASE SUMMARY

History

- 50 year old female
- 5 week history of:
  - Fevers
  - Night sweats
  - Rigors
  - Lethargy
  - Loss of appetite
  - Vomiting
- She had returned to the UK 4 weeks ago from a trip to Ethiopia
- She stayed for 7 weeks in Ethiopia, but only took malarial prophylaxis for the first 4 weeks
- She had no other symptoms to suggest a source of her fever

Examination

- Temperature 39.6º Celsius
- Blood Pressure 88/50mmHg
- Otherwise full examination unremarkable

Investigations

- White Cell Count 3.59 x10^9/L (3.40 – 8.40)
- **Neutrophil Count 1.51 x10^9/L** (1.60-4.60), normal eosinophil count
- Platelet Count 242 (150-400)
- **Albumin 29g/L** (35-50)
- **Alkaline Phosphatase 211 IU/L** (30-130)
- **C-reactive Protein 109mg/L** (<5)
- Blood Cultures negative after 48 hours incubation
- CXR showed no consolidation

- OptiMAL-IT Rapid Malarial Test (Malarial Parasite Antigen screen (MPS)) **positive.** ***"Plasmodium Falciparum detected"*** ***(Figure 1)***
- Blood film - **No malarial parasite seen on film** ?low parasitaemia
  - This was sent for PCR

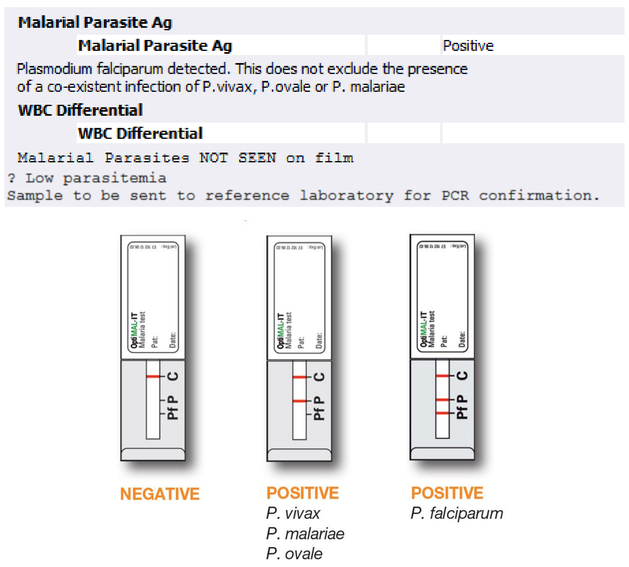

Figure 1. The patients OptiMAL-IT test results and a picture showing how the results are interpreted [2]

Management

- A diagnosis of Malaria seemed plausible
- She was **given a 3 day course of oral Artemether-Lumefantrine** (Riamet)
- 3 subsequent MPS detected plasmodium falciparum – but no parasites seen on blood film

Subsequent Course

- She remained an inpatient because of persistent vomiting
- She also had **persistent fevers** despite completing a treatment course of Malaria with Riamet ***(Figure 2)***

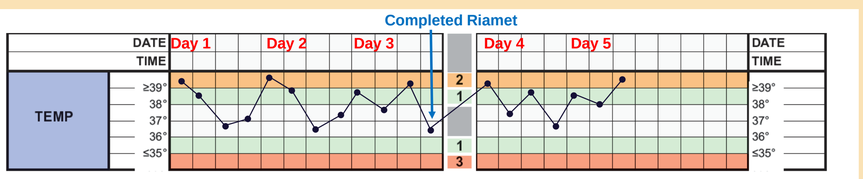

Figure 2. The patients temperature chart since admission (reconstructed)

- We re-explored her history. Her vomiting occurred over 1 hour after taking the Riamet tand she had not missed any doses
- Further questioning revealed she had **drank unpasteurized camels milk** frequently in Ethiopia
- Further blood cultures and stool samples were sent and the laboratory informed of a possible case of Brucellosis ***(Figure 3)***

CASE SUMMARY Continued

- On day 6, a blood culture flagged positive with a **gram negative cocco-bacillus**
- She commenced empirical therapy for Brucella with Rifampicin, Doxycyline and additional Gentamicin for the first week

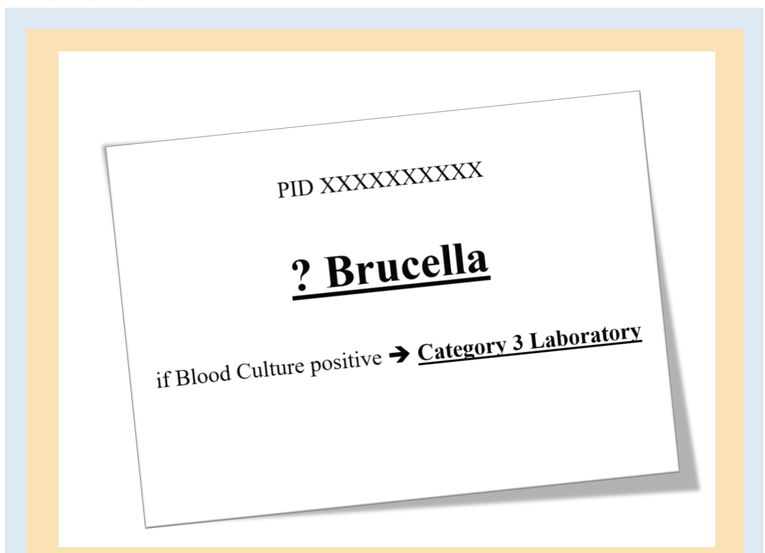

Figure 3. This sign was put on the blood culture incubator to inform the laboratory staff of a possible high risk sample (modified for confidentiality)

- Brucella species was confirmed on 16S PCR within the laboratory ***(Figure 4)***
- Serology was consistent with a diagnosis of acute brucellosis (IgM >2560, IgG 20) ***(Figure 4)***
- The animal laboratory **confirmed growth** of fully sensitive *Brucella melitensis* ***(Figure 4)***

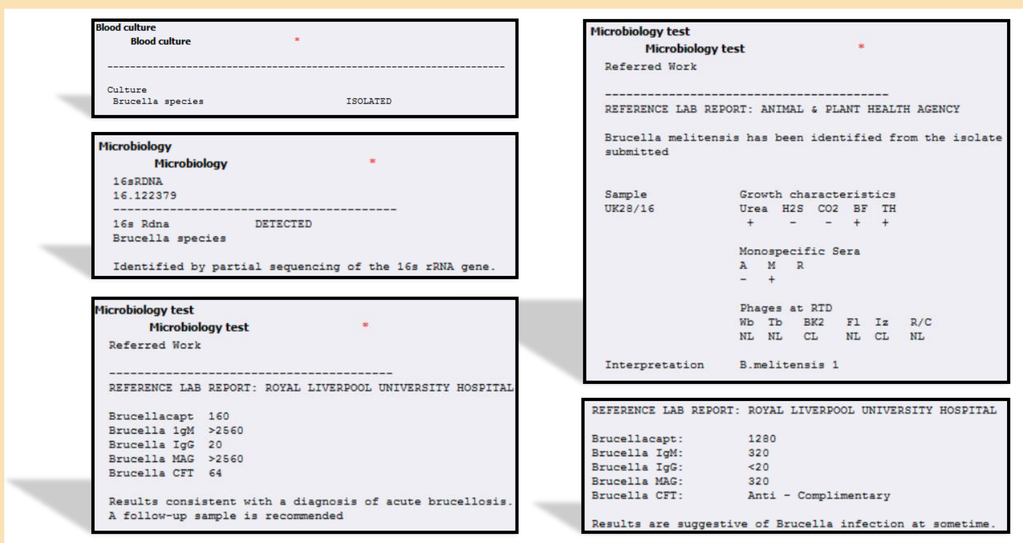

Figure 4. Blood results confirming the diagnosis of *Brucella melitensis causing acute Brucellosis*, with acute and convalescent serology

- There was no secondary organ involvement
- She completed a 3 month course of Rifampin and Doxycycline without complications
- PCR from the reference laboratory **did not detect Plasmodium DNA to suggest malaria**

DISCUSSION

- Positive MPS with no parasites seen may reflect
  - Low level parasitaemia – PCR methods can confirm the diagnosis
  - False-positive result

- OptiMAL-IT MPS has a reported sensitivity of >90% in patients with a parasite count of >1000/ul[3]
- Other rapid malarial testing kits have similar sensitivities reported[3]

- MPS detects **monoclonal antibodies** that bind to **active plasmodium LDH**

- False-positive MPS results have been reported in patients with **high circulating heterophile antibodies (ANA and Rheumatoid Factor)** with rates of up to 6.5%[4,5]

- There are a few reports of false-positive MPS in patients with **Hepatitis C, Dengue, Trypanosomiasis, Leischmaniasis, Schistosomiasis, Tuberculosis, Salmonella Typhi and Toxoplasmosis**[4] ***(Figure 5)***

- Our patient was negative for ANA, Rheumatoid Factor and Hepatitis C.

- There are no published reports of *Brucella melitensis* infection causing a false positive MPSThis patient had a false positive MPS

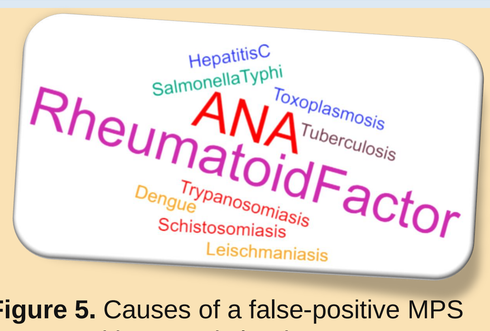

Figure 5. Causes of a false-positive MPS expressed in a word cloud

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CONCLUSION

- When a diagnosis does not respond as expected, it is important to re-evaluate the diagnosis and reconsider other differential diagnoses

- One should consider a possible false-positive result clouding the picture in such cases, as no test is 100% sensitive and specific