

Cryptic Disseminated Tuberculosis: An Often Missed Diagnosis

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Cryptic disseminated tuberculosis is an insidious form of presentation which mainly affects middle aged and elderly. Often the diagnosis is missed because possibility of tuberculosis is not considered. Lassitude, loss of weight, chronic ill health in the aged are erroneously attributed to some co-existent chronic disease or presumed occult tumours. Diagnosis is particularly difficult because choroidal tubercles are often absent, miliary pulmonary mottling may not be seen on chest radiography and the tuberculin test may be negative. The clinical features are often so non-specific that the diagnosis is frequently made only at autopsy. We report two such cases in one of which the diagnosis could only be confirmed post-mortem.

Case 1

A 72 year old lady, known diabetic and hypertensive for seven years initially presented with one week history of fever with chills. There were no positive physical signs on examination. She gave history of an episode of unresponsiveness about a week back which was attributed to hypoglycemia by her general practitioner and apparently she responded to intravenous glucose. She was on chlorpropamide 250 mg b.d. and methyl dopa 250mg b.d. Her initial investigations revealed a hemoglobin of 13.3 gm/dl, WBC count 5000/cmm with 64% neutrophils and a platelet count of 190,000/cmm, ESR 30 mm in first hour, RBS 174 mg/dl, BUN 8 mg/dl, creatinine 0.7 mg/dl, Na 122 mmol/L, K 4.2 mmol/L. Total bilirubin 1.0 mg/dl, SGPT 173 i.u./L (3-33) and alkaline phosphates 246 i.u./L (29-132). Her chest x-ray was normal. An ultrasound of abdomen revealed mild splenomegaly and a bone marrow aspirate showed atypical lymphocytes. In view of history of an episode of unresponsiveness, a CT scan of brain was done which showed cerebral atrophy. Peripheral blood smears were negative for malarial parasite. A working diagnosis of enteric fever was made and after collecting blood and bone marrow specimens for culture and sensitivity, she was started on oral ofloxacin and was discharged on patient's request. At the time of discharge her serum sodium was 124 mmol/L After a few days she was readmitted to another hospital with fever, hyponatremia and altered state of consciousness. She was treated with antibiotics and had a couple of episodes of hypoglycemia. She was again discharged and readmitted within 24 hrs due to episodes of unresponsiveness. On this occasion a CSF analysis was reported normal; all the blood and urine cultures were negative. She was empirically started on dexamethasone as well and discharged. While at home she was mostly in bed with eyes closed, minimal communication and complained of lassitude and lethargy. She developed incontinence of urine and was brought to our medical centre with fever, episodic unconsciousness and incontinence of urine. On examination she was drowsy but responding with eye-opening and moaning on repeated verbal and painful stimuli. There were no focal signs on neurological examination and no neck stiffness. Liver was palpable 5 cm below right costal margin. Her initial investigations showed hemoglobin 13.6 gm/dl, WBC 16.0x10⁹/L with neutrophils 82%, platelets 1 18x10⁹/L, Na 114 mmol/L, Cl 86 mmol/L, K 3.3 mmol/L, HCO₃ 20.7 mmol/L, RBS 103 mg/dl, BUN 15 mg/dl and creatinine 0.5 mg/dl. Urine osmolality was 400 mosm/kg, serum osmolality 231 mosm/kg and S. urine spot Na 89 mmol/L Prothrombin time 15/13 seconds, APf131/33 seconds, T. bilirubin 1.5 mg/dl, SGPT 210 i.u./L, Alk. phosphates 234, S. albumin 2.6 gm/dl and S. globulin 2.6 gm/dl, S. calcium 7.2 mg/dl, phosphorus 2.9 mg/dl and uric acid 2.8 mg/dl.

In essence, this lady presented with a prolonged illness manifesting as intermittent fever not responding to empirical antibiotics, SL&DH and fluctuating level of consciousness. An assessment of atypical infection including granulomatous infection, occult malignancy or autoimmune disorder with metabolic encephalopathy was made. A repeat CT scan of brain was normal apart from cerebral atrophy; all

routine aerobic and anaerobic cultures of blood, bone marrow and urine were negative and Brucella and Monospot serology for infectious mononucleosis was within normal range. She was managed with fluid restriction and insulin for her diabetes mellitus and showed improvement in her level of consciousness. No antibiotics were given. Her repeat liver function tests showed total bilirubin of 0.9 mg/dl, SGPT 65 i.u./L and Alk. phosphatase 156 i.u./L. On the 5th post-admission day she developed grand mal seizure and again became less responsive. Her serum Na⁺ was 130 mmol/L and there was no hypoglycemia. She was given diazepam and later maintained on phenytoin sodium. She continued to spike fever up to 39°C but was more alert for next 36 hrs. Although there was no apparent blood loss, her repeat hemoglobin was 9.5 gm/dl, WBC 11x10⁹/L and platelets 88x10³/L. The bone marrow trephine was normal with no granulomas or malignant cells seen. She was empirically started on third generation cephalosporin and metronidazole. In view of continuing fever, stupor and SIADH, a CT chest was performed which showed a pleural based soft tissue mass located at the basal portion of right hemithorax which could be a loculated pleural collection or mesothelioma. A percutaneous needle biopsy of the lesion showed acute and chronic inflammatory cells as well as large histiocytic cells with plentiful eosinophilic cytoplasm. No granulomas were seen. A CT of abdomen and pelvis showed some distortion of caecum but was otherwise unremarkable. At this point her platelet count further dropped to 58x10⁹/L. An electroencephalogram was consistent with metabolic encephalopathy, most probably hepatic. A liver biopsy was considered but in view of thrombocytopenia, management of hepatic encephalopathy was started and liver biopsy deferred. An arterial blood ammonia level was 121 (17-80 ng/dl) and a repeat CSF analysis showed proteins 108 mg/dl, Glu 77 mg/dl, WBC 04/cmm. Although she was on subcutaneous heparin, she developed episodes of tachypnea with hypoxia; she developed ventricular fibrillation followed by asystole and expired on 15th post-admission day. A postmortem liver biopsy showed multiple centrally caseating granulomas composed of epithelioid cells, multinuclear giant cells, lymphocytes and plasma cells. No acid fast bacilli seen, the picture being consistent with tuberculosis.

Case 2

A 41 year old estate agent with history of hemorrhoids was admitted with complaints of increased bleeding per rectum, abdominal distension and dyspnea for 21 days. He was unable to climb a flight of stairs which he attributed to increasing abdominal distension. On examination, this young man was dyspneic on minimal exertion, was markedly anaemic and pale. On abdominal examination, the abdomen was tense, umbilicus central and everted; liver was palpable 3 cm below right costal margin with a span of 16 cm and spleen was palpable 15 cm below the left costal margin. The laboratory investigations showed a hemoglobin of 4.4 gm/dl, WBC count of 1.0x10⁹/L (35%N), platelets 76x10⁹, reticulocyte 3.0% with microcytosis, anisocytosis, polychromasia, rouleaux formation and pancytopenia. Bone marrow aspirate and trephine showed mild suppression of myeloid series with 2% blast cells. Erythropoiesis was dyserythropoietic. No malignant cells or granulomas or Leishman-Donovan bodies identified. Serum ferritin level was 6.1 ng/ml (25-400). Other investigations showed total bilirubin 1.4 mg/dl, SGPT 15 i.u./L, alkaline phosphatase 88 i.u./L (28-124). Total protein 7.2 gm/dl, albumin 3.2 gm/dl, globulin 4.0 gms/dl, BUN 12 mg/dl (6-16), creatinine 0.9 mg/dl, Na 134 mmol/L, K 4.4 mmol/L, chloride 111 mmol/L, bicarbonate 18.7 mmol/L. He was treated with folic acid and ferrous sulphate for iron deficiency anaemia but in view of hepatomegaly and massive splenomegaly and hypersplenism, he was referred to surgeons for elective splenectomy. On histopathological examination, the spleen was grossly enlarged, weighing 3.4 kgs. Serial sections did not show any area of infarction or tumour. The histology showed increased amount of red pulp and decreased white pulp with marked congestion. No evidence of granulomas or malignancy seen. The features were reported to be consistent with tropical splenomegaly syndrome. Two weeks post-splenectomy he developed high grade fever. On examination his chest was clear. Abdominal examination revealed soft, non-tender abdomen with liver palpable 9cm below the right costal margin and it was smooth and non-tender. Laboratory investigation showed haemoglobin 11.3 gm/dl, ESR25,

WBC $13 \times 10^9/L$ with 79% neutrophils and platelets $836 \times 10^9/L$. An ultrasound and CT scan of abdomen and pelvis did not reveal any abscess or collection in the peritoneal cavity. After drawing blood cultures he was started on benzylpenicillin, metronidazole and cefotaxime. As part of work-up of pyrexia of undetermined origin, an echocardiogram revealed mitral and tricuspid prolapse and a small echodensity on the posterior leaflet of mitral valve. Multiple blood cultures taken when temperature spiking did not grow any organism. During 10 days of his hospitalization he continued to have 38-39°C fever and his liver enlarged further to 18 cm below right costal margin. In view of enlarging liver size and no response to antibiotics, a liver biopsy was performed which showed markedly dilated sinusoids with marked lymphocytosis. Large areas of caseating granulomatous lesion were seen, consistent with tuberculosis. He was treated on anti-tuberculosis treatment. He became afebrile in three weeks time and gained 7 kg in weight over next 4 months.

Discussion

These two cases illustrate the importance of considering tuberculosis in the differential diagnosis of PUO, hepatosplenomegaly and hematological disorders especially in the endemic area although cases have been reported from elsewhere as well. The clinical picture of cryptic disseminated tuberculosis is, by definition, non-specific. It occurs more frequently in the elderly¹⁻³ and this age group is at particular risk of death from tuberculosis^{4,5}. In a patient with a combination of two or more of the more commonly encountered features, i.e., prolonged pyrexia of unknown origin, hepatomegaly, splenomegaly and abnormal chest signs, the clinician should be alerted to the possibility of cryptic disseminated tuberculosis. Choroidal tubercles when present are pathognomonic; however, were not detected in our patients. This is not surprising as choroidal tubercles are known to be uncommon in non-caucasians with tuberculous meningitis or miliary T.B⁵. The chest radiography was normal in both our patients, as has been reported in other series^{2,6,7} as well. As seen in both our patients, a wide range of hematological abnormalities, many of which may reflect bone marrow disease have been described in patients with tuberculosis⁷. These include leukemoid reaction, pancytopenia, agranulocytosis, aplastic anaemia, thrombocytopenia, leuco-erythroblastic anaemia, polycythemia and eosinophils. As in first case, abnormalities in the liver function tests reported^{2,8,9} include raised levels of alkaline phosphatase and Gamma-GT and hypoalbuminemia. As in the first case, hyponatremia in tuberculosis was first described in 1930¹⁰ and is thought to be due to SJADH¹¹ but may also be due to adrenal hypofunction. The diagnosis of tuberculosis may often be difficult because of non-specific symptoms and the absence of typical radiological findings. It is important to have a high index of suspicion and start treatment early. There is often no harm in starting anti-tuberculous treatment while awaiting the results of investigations and this may prevent a fatal outcome^{12,13}.

References

1. Edlin, G.P. Active tuberculosis unrecognized until necropsy. *Lancet*, 1978;1:650-52.
2. Prose, S., Benatar, SR.. Disseminated tuberculosis - a study of 62 cases. *S.Afr.J.*, 1980;58:835-42.
3. Bobrowitz, I.D. Active tuberculosis undiagnosed until autopsy. *Am.J.Med.*, 1982;72:650
4. MacKay, AD. and Cole, RB. The problems of tuberculosis in the elderly. *QJ.Med.*, 1984;53:491-5-10.
5. Tandon, P.N. Tuberculous meningitis (cranial and spinal). In: P.J. Vinken, G. Bruyn, eds. *Handbook of clinical neurology*, vol. 3 infections of the nervous system. Part . Amsterdam, North Holland PublishingCo., 1978, pp. 195-262.
6. Bottiger, L.E., Nordenstram, H.H. and Weston, P.O. Disseminated tuberculosis as a cause of fever

of obscure origin. *Lancet*, 1962;1:19.

7. Oswald, N.C. Active tuberculosis and granulocytic disorders. *Br.Med.J.*, 1963;2:1489-96.

8. Mum, P.W. Miliary tuberculosis in the chemotherapy era: with a clinical review in 69 American adults. *Medicine*, 1972;51:139-55.

9. Yu, U.L., Chow, W.H., Humphreys, M.J., et al. Cryptic miliary tuberculosis. *Q.J.Med.*, 1986;59:421-28.

10. Winkler, A.W. and Cranksbaw, O.F. Chloride depletion in conditions other than Addison's disease. *J.Clin.Invest.*, 1938;17: 1-6.

11. Vorberr, H., Nassry, S.G., Pallet, R., et al. Antidiuretic principle in tuberculous lung tissue of a patient with pulmonary tuberculosis and hyponatremia. *Intern. Ann. Med.*, 1970;72:383-87.

12. Treip, C. and Meyers, D. Fatal tuberculosis in a general hospital. A diagnostic problem. *Lancet*, 1959;1:164-67.

13. Proudfoot AT., Akhtar, A.J., Douglas, A.C. and Horne, N.W. Miliary tuberculosis in adults. *Br.Med.J.*, 1969;2:273-76.