An unconscious eighteen-year-old female

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, NEW DELHI

THE CASE

An 18-year-old female was brought unconscious to the All India Institute of Medical Sciences, New Delhi on 10 July 1990. For the previous one and a half months she had had high grade intermittent fever associated with chills, rigors and a dull continuous headache. During afebrile periods she had started behaving abnormally—crying out loudly, tearing at her clothes and moving all four limbs violently. These episodes lasted for about one hour after which the patient used to become unconscious. There was no history of tonic or clonic movements, tongue biting and urinary or faecal incontinence.

Her high intermittent fever, associated with chills and rigors, lasted one and a half hours, and subsided with profuse sweating. Initially the fever was associated with pain in the mid-lumbar region and in the right flank and this later became localized to the epigastrium. She received treatment from a local doctor, the nature and duration of which were not known. After she had had these symptoms for one month she was admitted to the Jawaharlal Nehru Medical College Hospital in Aligarh. Cerebrospinal fluid (CSF) examination there showed a protein level of 300 mg/dl, sugar of 150 mg/dl and chlorides of 680 mg/dl. The cell count was not mentioned in the report. The patient was moribund but afebrile on admission. On 27 June 1990, she developed high grade fever again and became unconscious. There was no history of head trauma, photophobia, ear or nasal discharge, or neck pain. There was no cough, expectoration, jaundice, biliary colic or bleeding from abnormal sites.

At the time of admission to the All India Institute of Medical Sciences, she was afebrile and comatose. Her pulse rate was 110 per minute of good volume and the blood pressure was 120/70 mmHg. The cardiovascular and respiratory systems were normal. Abdominal examination did not reveal any organomegaly or abnormal masses. Examination of the nervous system revealed that she was unconscious, winced after painful stimulation and moved only her right upper limb. Her pupils were of normal size and reacted to light. The fundi were normal. Examination of her motor system showed a normal tone in her right upper limb, but the other limbs were hypotonic. The tendon reflexes were increased in all the limbs and the abdominal reflexes were absent. The plantar response was flexor on the right side and extensor on the left. Signs of meningeal irritation were present.

Investigations done at the time of admission showed a haemoglobin of 6.3 g/dl, a total leucocyte count of 4000 per cmm and the differential count showed 66% neutrophils, 30% lymphocytes and 4% eosinophils. The erythrocyte sedimentation rate was 54 mm in the first hour. Her platelet count was 150,000 per cmm, blood sugar 132 mg/dl and blood urea 30 mg/dl. The serum sodium was 122 mEq/L and potassium 3 mEq/L. The total proteins were 6.0 g/dl (albumin 2.9 g/dl and globulin 3.1 g/dl). The serum bilirubin was 0.6 mg/dl, the serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were 20 and 28 IU/L respectively. The serum alkaline phosphatase was 204 KAU, serum calcium 7 mg/dl and phosphate 4.6 mg/dl. Urine examination showed 2+ albumin and microscopic examination revealed 5 to 8 pus cells and 15 to 20 red blood cells per high power field. CSF examination showed a clear fluid with 10 white blood cells per high power field which were mainly lymphocytes. The protein level was 122 mg/dl, sugar 98 mg/dl and the globulins were positive. A computerized tomographic (CT) scan of the head was taken at the time of admission, a provisional diagnosis was made and treatment started. On the second day after admission she developed hypotension with a systolic blood pressure of 60 mmHg which was corrected by the administration of intravenous fluids. However, she again developed hypotension later on the same day, the systolic blood pressure fell to 30 mmHg and she was given dopamine infusion. She was shifted to the intensive care unit and connected to a ventilator when she had a cardiorespiratory arrest and could not be revived.

DIFFERENTIAL DIAGNOSIS

Col. S. Venkataraman: This patient had intermittent high grade fever associated with chills and rigors and a dull continuous headache for about one and a half months before admission. This might mean she had an infection such as malaria, tuberculosis, amoebiasis (especially of the hepatic variety), typhoid or one of the other numerous causes of pyrexia. Pain in the epigastric region would suggest conditions like urinary tract infections and hepatobiliary diseases such as amoebic liver abscess or cholangitis with septicaemia. These features could also suggest tuberculosis of the spine or the retroperitoneal lymph nodes.

The abnormal behaviour during the afebrile period in this patient could have been due to any of these conditions:

1. Partial complex seizures
2. An episodic reaction that occurs in certain sociopaths
3. Haemorrhagic leucoencephalitis
4. Herpes simplex encephalitis
5. Traumatic necrosis
6. Wernicke's encephalitis
7. Aneurysm of the circle of Willis
8. Hypphyseal adenomas
9. Temporal intracranial space occupying lesions
10. Acute or chronic neurological disease
11. A functional disorder

The report of the CSF examination at Aligarh does not include either the cell count or the results of the bacteriological examination. The corresponding blood sugar level is not available to account for the raised CSF sugar level which was 150 mg/dl. This can occur only in a patient who has diabetes mellitus or is on intravenous glucose. The differential diagnosis that should be considered when she later became febrile and unconscious would include infective conditions such as acute meningitis or encephalitis, cerebral malaria, brain abscess and sepsicemia as well as non-infective conditions such as heat hyperpyrexia and pontine haemorrhage.

On admission to the All India Institute of Medical Sciences, she was afebrile but comatose and responded only to painful stimuli. The tachycardia could be explained by anaemia in the absence of any cardiac disease. The blood pressure was normal.

Systemic examination at that time revealed only a focal neurological deficit while the other systems were normal. The findings of the neurological examination with normal cranial nerves, a normal light reflex and optic fundi suggest that there was no structural brain stem lesion involving the consciousness-maintaining centres. This could then be explained by bilateral cerebral dysfunction due to metabolic encephalopathy. The motor findings—the normal tone in the right upper limb, hypotonia of the other limbs, increased tendon reflexes in all the four limbs and the upgoing plantar response on the left side and meningeal signs (recorded for the first time) would suggest cerebral dysfunction rather than a metabolic encephalopathy. I shall discuss the neurological localization a little later.

Investigations revealed anaemia and normal total and differential leucocyte and platelet counts. The blood sugar was 132 mg/dl and I presume this was a random sample. The other important findings include hyponatraemia and a low normal serum potassium. There was no suggestion of any previous fluid or electrolyte loss. The albumin–globulin ratio was altered. There was no evidence of hepatocellular dysfunction as noted by the serum bilirubin and transaminase levels. However, the serum alkaline phosphatase of 204 KAU (normal 4–13 KAU) was raised almost fifteen fold. Such high levels of alkaline phosphatase are usually encountered in cholestatic disease of the liver which may have been present in this patient but non-hepatic disorders such as Paget's disease of the bone, osteomalaclia, metastatic bone disease and malignancy can also result in such high levels of serum alkaline phosphatase. 5'-nucleotidase estimation might have helped to determine whether the alkaline phosphatase was of hepatic or bony origin.

The urine analysis suggests that a renal disease exists which could be urinary tract infection or interstitial nephritis.

The CSF examination done at the All India Institute of Medical Sciences which showed a high sugar level (98 mg/dl against a normal of 60–80 mg/dl) is actually explained by the high blood sugar level of 132 mg/dl. Mild lymphocytic pleocytosis of the type seen in this condition can occur in the following conditions:

1. Meningitis (viral, bacterial, fungal, chemical and carcinomatous)
2. Parameningeal infections
3. Poliomyelitis, herpes zoster
4. Encephalitis of different types
5. Cerebral abscesses
6. Sinus thrombosis
7. Cerebral tumour
8. Multiple sclerosis
9. Following cerebrovascular accidents and subarachnoid haemorrhage
10. Post-traumatic
11. Lead poisoning

In the presence of meningeal signs, various types of chronic meningitis (tuberculous, fungal and carcinomatous) should be considered.

A provisional diagnosis was made and treatment started (which I presume was with anti-tuberculous drugs). The hypotension that developed from the second day of admission appears to have been central in origin since there is no history to suggest hypovolaemia or pump failure.

I shall now discuss the neurological localization. The patient had meningeal signs, was febrile intermittently and was unconscious. There was no sign of raised intracranial tension. The cranial nerves were normal. However, the abnormal behaviour with afebrile periods suggests a temporal lesion which cannot be lateralized on these points alone. The motor signs revealed pareses of the left upper and right lower limbs. Evidence of pyramidal tract involvement was elicited on the left side but on the right side the weakness could have been either of the upper or lower motor neurone type. If upper motor neurone weakness was present, then the lesion could be in the anterior cerebral artery territory or in the parasagittal region, around the paracentral lobule. A temporal lobe lesion has already been considered and this taken with the pyramidal signs, would have been on the right side. If cerebral lesions are to explain the focal motor deficits and unconsciousness, then the lesions should be multiple and bilateral. If the right lower limb weakness is diagnosed to be of the lower motor neurone type, then a radicular lesion would explain the weakness and the flexor plantar response on the right side. In this instance one might consider a lumbar lesion or tuberculous arachnoiditis.

Another diagnosis could be malignant deposits in the lymph nodes but I will make no further guesses at this stage. Investigations to examine the spine and abdomen were not done, so with the data available, I would conclude that the focal neurological deficit suggests bilateral cerebral disease and the CSF picture suggests a chronic meningitis and meningoencephalitis.

Now let us discuss the radiological findings. The chest X-ray reveals a normal thoracic cage and lung parenchyma. There is a group of calcified soft tissue masses outside the lung fields, in the hilar regions. There is no enlargement of the mediastinal shadow and the heart is normal. The CT scan reveals two high attenuating lesions bilaterally over the caudate nucleus area (on the left more than the right) with mild dilatation of the lateral and third ventricles. Contrast studies reveal further enhancement of these two lesions and further lesions over the right basal ganglia, left anterior temporal and deep temporo-parietal regions. The lesions enhance with low attenuation in the centre of some of them.
There is no shift of the midline. The differential diagnosis of such multiple lesions on the CT scan includes the following:

1. Infections
   - Multiple tuberculomas
   - Brain abscess
   - Cysticercosis
   - Fungal lesions
   - Syphilitic lesions
   - Protozoal lesions (amoeba, toxoplasma)

2. Non-caseating granulomas
   - Sarcoïdosis

3. Tumours
   - Primary (gliomas, lymphoma)
   - Secondary (choriocarcinoma, non-Hodgkin's lymphoma, nephroblastoma, renal carcinoma, neuroblastoma)

4. Vascular lesions
   - Malformations
   - Granulomatous angiitis

5. Other conditions
   - Phakomatosis

To sum up, this was an 18-year-old girl with fever for one and a half months, lumbar and right flank pain, abnormal behaviour, multiple focal neurological signs, a CSF showing pleocytosis, elevated proteins and a normal sugar, multiple contrast-enhancing lesions on CT scan and calcified lymph nodes on plain chest X-ray.

The clinical features suggest a chronic meningitis. In my practice, I would consider tuberculosis, cystickercosis, fungal meningitis and carcinomatous meningitis. However, I shall take into consideration the multiple enhancing lesions seen in the CT scan and discuss the various possibilities.

Firstly, tuberculosis is the commonest disease that might explain this clinical picture. Most of the findings including proteinuria, high alkaline phosphatase levels, lumbar and flank pain, weakness of the right lower limb and of course the neurological features can be explained by tuberculous meningitis and tuberculomas. The terminal event of hypotension could be due to adrenal failure. Further, if the high attenuating lesions on CT scan were due to multiple haemorrhages, tuberculosis could also account for them.

Of the metastatic lesions, most show a homogeneous enhancement on CT scan. Ring enhancement occurs in some cases especially due to necrosis, when the tumour outgrows its blood supply. Choriocarcinoma is one such tumour. However, in this case details regarding the marital status and human chorionic gonadotrophin levels are not known. The other possible diagnoses such as metastatic hypernephroma, neuroblastoma and primary central nervous system lymphoma can be excluded on clinical and other findings.

Vascular abnormalities are not likely in this case. Amongst the systemic vasculitides, polyarteritis is unlikely because of the absence of hypertension. Granulomatous angiitis (isolated angiitis of the central nervous system) has to be considered in the differential diagnosis of culture negative chronic meningitis. This disease, of unknown aetiology, affects small intracranial vessels and medium sized arteries. Focal neurological deficits occur due to multiple haemorrhages and infarcts. It affects the young and middle-aged and the presentation is generally that of increased intracranial tension with or without meningitis.

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**COL S. VENKATARAMAN’S DIAGNOSES**

- Disseminated tuberculosis
- Choriocarcinoma
- Angiitis, possibly granulomatous

**CLINICAL DISCUSSION**

**DR C. SARKAR:** Please clarify whether by disseminated tuberculosis you mean multiple tuberculomas?

**COL S. VENKATARAMAN:** I said that as far as the CT findings are concerned, there could be multiple tuberculomas in the brain, with renal tuberculosis.

**DR S. C. DASH:** With high grade fever and chills and profuse sweating would you also consider a pyogenic brain abscess? How about neurobrucellosis which can cause these symptoms, and very rarely a brain abscess? I would say that, as this is a clinico-pathological conference, the chances of a diagnosis of tuberculosis are low. I would also consider lymphoma, as the alkaline phosphatase is raised; there is proteinuria and microscopic haematuria.

**COL S. VENKATARAMAN:** Brucellosis would be part of the differential diagnosis of a high fever, but not of a brain abscess. I did not consider acute meningitis as the CSF was clear.

**DR S. C. TIWARI:** You have not discussed the hyponatraemia. The patient was unconscious and then regained consciousness. In any cerebral lesion, without treatment, such a phenomenon would be unusual. What was the cause of hyponatraemia? Could there have been inappropriate secretion of the antidiuretic hormone (ADH)? The alkaline phosphatase is markedly raised. There is sterile pyuria. Would you consider the possibility of Hodgkin’s disease?

**COL S. VENKATARAMAN:** I have no explanation for the hyponatraemia and pyuria. I have discussed lymphomas of the central nervous system. On the CT scan, there are bilateral lesions in the basal ganglia which may one see in a lymphoma.

**DR V. RAMALINGASWAMI:** In your slide of differential diagnoses, you mentioned cysticercosis but did not comment further. In your three differentials, I do not understand how you explained the very high alkaline phosphatase, unless there was a massive involvement of the liver without any clue being given to us in the protocol. The slightly depressed calcium level and raised alkaline phosphatase might suggest osteomalacia but then you would have to consider two diagnoses. Lastly, a viral infection. Have you considered herpes simplex?

**COL S. VENKATARAMAN:** Yes, cysticercus meningitis is possible. However, the CT scan excludes cysticercosis in which the lesions are of pinhead size, ring-enhancing or disc-enhancing. In our country we do not see the so-called conglomerate basal meningeal collections, but only the parenchymatous forms. Soft tissue calcification is much less common here than is reported in the western literature. I am at a loss to put all these findings together. I still stick to tuberculosis, as micro-tuberculous hepatitis may cause a raised alkaline phosphatase. Herpes was brought in as a differential diagnosis, but the course of herpes is not so long. Are you sure that the alkaline phosphatase levels are expressed in KA and not IU.

**DR KAMESHWAR PRASAD:** This 18-year-old girl had been married only three days before she became ill. When she first came, the diagnosis seemed to be easy. She had had a one and a half month history of fever, headache and altered
sensorium, was unconscious for 15 days with focal neurological deficits and meningeal signs. We made a diagnosis of chronic meningitis and started anti-tuberculous treatment. When the contrast enhanced CT scan and plain scans were done, they were interpreted to be multiple infarcts. This tallied well with our clinical diagnosis of chronic meningitis and the anti-tuberculous treatment was continued.

However, the results of some of the investigations did worry us. One was the extremely high alkaline phosphatase level (in KAU and not IU). Some of us wondered whether she had a malignancy and we decided to repeat the test. The patient died before the results reached us.

The sterile pyuria goes along with a: dissem-inated tuberculosis. Hyponatraemia is encountered frequently in this condition possibly due to inappropriate ADH secretion.

She was with us for only three days and during that time she was unconscious. We had been giving steroids for adrenal failure from the beginning, and later dopamine, to no avail.

Our diagnosis, at the time of death, was disseminated tuberculosis.

PATHOLOGICAL DISCUSSION

Dr C. Sarkar: Consent for complete autopsy was obtained, and this was performed two hours after death by my colleagues Drs M. B. Prakash and Debesh Pal. The brain weighed 1190 g. The CSF was clear. The dura and venous sinuses were normal. The leptomeninges on the superolateral aspect of the brain as well as over the cerebellum and brain stem were mildly opaque.

On serial sectioning, soft necrotic friable areas involving the caudate nucleus, part of the anterior limb of the internal capsule and the lentiform nucleus, especially the putamen, were seen on both sides (Fig. 1). The left temporal lobe showed a small, ill-defined, grey-white area about 0.5 cm in diameter. The circle of Willis was grossly normal. Multiple sections of the brain were examined microscopically and three distinct lesions were found. The first was a chronic meningitis. The meninges were infiltrated with chronic inflammatory cells chiefly lymphocytes, plasma cells and histiocytes (Fig. 2a). In addition, ill-defined granulomas consisting predominantly of epithelioid cells were seen. There was no necrosis or fibrinous exudate. Stains for acid-fast bacilli were strongly positive in the meninges.

The next important finding was vasculitis (Fig. 2b). Meningeal vessels of all sizes had lymphocytic infiltration of their walls. The left middle cerebral artery showed vasculitis with subintimal fibrosis and partial occlusion of the lumen. The third finding in the brain was multiple healing infarcts (Fig. 3a) in the territory of the middle cerebral artery, both basal ganglia and the left temporal lobe. One infarct was also seen in the periventricular region (Fig. 3b) of the right temporal lobe.

Multiple tuberculous granulomas were also identified in the lungs (Fig. 4a), liver (Fig. 4b), spleen, lymph nodes and serosal surfaces of the intestines, uterus, fallopian tubes, ovaries and omentum (Fig. 4c). Acid-fast bacilli could be demonstrated in sections from some of these organs. We concluded that this patient had miliary tuberculosis.

Tuberculosis is still a widespread disease in India. Haematogenous dissemination results in miliary tuberculosis. It is well recognized that about 10% to 20% of miliary tuberculosis is diagnosed only at autopsy.

Neurotuberculosis is a frequent and serious complication of the infection. Tuberculous meningitis accounts for about 80% of cases of tuberculosis of the central nervous system. However, only 10% of cases of miliary tuberculosis present as tuberculosis meningitis.

The initial lesion in the central nervous system is a ‘Rich’ focus first described in 1933. This is a small granuloma or caseous focus just below the brain surface usually located
around the interpeduncular fossa notably in the subthalamic regions, the floor of the third ventricle and the temporal lobes. Bacilli are thus discharged directly into the subarachnoid space resulting in meningitis. This is the possible reason for the brunt of the disease falling on the basal meninges.

The vascular changes in tuberculosis of the brain vary with the size of the blood vessels, the severity and duration of the disease and the treatment status of the patient. The terminal portion of the internal carotid artery and the proximal 2 cm of the middle cerebral artery in the Sylvian fissure are most frequently involved as assessed on gross and angiographic examination. The vertebrobasilar system, although equally bathed in the exudate, usually escapes. Microscopically, the vascular changes are always extensive involvement of the vessels (both arteries and veins) of different sizes. The adventitia is usually the first to become inflamed and this eventually progresses to necrotizing panarteritis with secondary thrombosis and occlusion. In treated cases, endarteritis with subintimal fibrosis (segmental or concentric) is more characteristic of the disease than necrosis. Although granulomas can be observed on the adventitia, caseous necrosis is rare. Meningeal vessels show varying degrees of phlebitis which may lead to thrombosis. In this case both fibrosis and vasculitis with thrombosis of the middle cerebral arteries were identified.

Parenchymal involvement by tuberculosis—tuberculomas—are reported in around 10% of cases whenever the meningeal exudate impinges on the bordering parenchyma. Reactive changes occur in the form of perivascular chronic inflamma-
tion, oedema, microglial reaction and gliosis. Thus the term tuberculous meningoencephalitis is fairly accurate.

There is a good correlation between the clinical and pathological findings in this case.

**AUTOPSY DIAGNOSIS**

- Miliary tuberculosis involving the lungs, liver, spleen, serosa over the small and large intestines, uterus, fallopian tubes, ovaries, gall bladder, omentum, mesentery, pleura, parabronchial and paraaortic lymph nodes, peritoneum and meninges.
- Involvement of the superolateral and basal surfaces of the brain with vasculitis and multiple healing infarcts involving the caudate nuclei, lentiform nucleus, temporal lobes, the paraventricular area and the right internal capsule.

**REFERENCE**


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