Case Report

A case of metastatic high grade neuroblastoma with undetected primary in adult presenting with soft tissue lumps and bilateral choroidal metastases

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ABSTRACT

An adult male patient got hospitalized with fever, anorexia, weight loss, generalized weakness, and visual problem. Examination revealed solitary axillary lymphadenopathy and soft tissue swellings over scalp and left shoulder. Tests detected severe anemia and raised erythrocyte sedimentation rate (ESR), lactate dehydrogenase, and uric acid. Magnetic resonance imaging (MRI) brain showed irregular soft tissue swellings both outside and inside the skull with pressure effect on brain. Fundoscopy revealed bilateral choroidal metastatic deposits with papilledema. Histopathology findings of biopsy from scalp mass and bone marrow were consistent with metastatic high grade neuroblastoma. No primary lesion was found on computed tomography (CT) scan of thorax, abdomen, and pelvis. There was also suggestion of paraneoplastic neuropathy. The patient responded fairly to chemotherapy. Neuroblastoma is usually known to be a childhood malignancy that often presents with vague symptoms or symptoms due to tumor mass or with metastatic or paraneoplastic features. Most common metastatic sites are bone, lymph node, liver, cranium, and chest. But in this case apart from bony and dural metastases there was also choroidal metastasis which is previously not reported in adults. Likewise, non-detection of primary tumor is also uncommon.

Key words: Choroidal metastasis, neuroblastoma, soft tissue swellings

INTRODUCTION

We are reporting a case of high grade neuroblastoma in an adult male who presented with metastases to bone, bone marrow, dura, soft tissue, and choroidal tissue in absence of detectable primary tumor. Metastases to bone, scalp, or dura as in our case are common in neuroblastoma.[1] But choroidal metastasis, that too bilateral, in adult patient is very rare and we could not find any case report mentioning such occurrence in available literature; although in pediatric population choroidal metastasis of neuroblastoma is common.[2-4] There was also suggestion of paraneoplastic peripheral neuropathy which also is rare. This case also shows that early diagnosis and aggressive treatment can be lifesaving.

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CASE REPORT

An 18-year-old nondiabetic, non-hypertensive male presented with complaints of on-and-off low grade fever, generalized weakness, bodyache, anorexia, and weight loss for 6 months. He had also developed a swelling over left shoulder and lately another over forehead on right side. There was no history of trauma, any addiction, or unprotected sexual exposure. He was unmarried and lived alone away from home and was jewelry worker by occupation. He had taken antitubercular drugs for a few days without any improvement.

On general examination there was severe pallor, malnutrition, raised temperature, and tachycardia. A solitary firm, non-tender, non-matted, fixed central left

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axillary lymph node of 2.5 × 1.5 cm size was palpable. There were multiple non-tender, immobile, firm swellings of varying sizes over scalp. Lymph node anywhere else, liver and spleen were not palpable. There was hypotonia, hyporeflexia, and weakness in all four limbs. All muscles, especially thigh muscles were tender.

After hospitalization, he developed rapidly progressive dimness of vision. Both pupils were semidilated and sluggishly reacting to light. Ophthalmoscopy showed papilledema and elevated lesions at paradiscal and parafoveal regions bilaterally.

Prehospitalization report showed a positive tuberculin test. After hospitalization, hemogram showed hemoglobin 5.8 g%, erythrocyte sedimentation rate (ESR) 160 mm, increased rouleaux formation. Erythrocytes were normocytic and normochromic. Serum lactate dehydrogenase (LDH) was 7,443 mg/dl and uric acid was 11.8 mg/dl. Other routine blood reports, e.g. blood sugar, liver function tests, urea, creatinine, and electrolyte level were within normal limits. Serum creatine kinase and aldolase levels were not raised. Skiagram of chest and ultrasound of abdomen and both thighs and cerebrospinal fluid study were noncontributory. Tests for human immunodeficiency virus, hepatitis B, and hepatitis C virus were negative. X-ray of left shoulder showed erosive lesion over scapula. MRI brain showed irregular soft tissue swellings both outside and inside skull with pressure effect on brain [Figure 1]. Fundoscopy revealed bilateral choroidal metastatic deposits with retinal edema and exudates [Figure 2]. There was also papilledema and retinal hemorrhage on both eyes. Fine needle aspiration cytology from scalp swelling was suggestive of malignant round cell tumor. Biopsy from axillary lymph node was inconclusive. Bone marrow aspirate was hypercellular with > 90% blasts and pseudorosette formation. Myeloid: erythroid ratio was >100:1. But immunophenotyping did not suggest any hematolymphoid malignancy. Histopathology of biopsy from scalp mass showed small round cells with scanty cytoplasm arranged in lobules with pseudorosette formation. The cells were positive for neuron-specific enolase (NSE) [Figure 3] and synaptophysin and negative for CD99 and chromogranin. Immunophenotyping from bone marrow biopsy material revealed the same findings. The findings were consistent with neuroblastoma. Contrast-enhanced CT (CECT) scan of thorax and abdomen revealed nothing significant except erosive changes in left scapula. Nerve conduction velocity test of all four limbs showed absent F wave and normal compound muscle action potential (CMAP) in median, ulnar, tibial, and common peroneal nerve (may be due to paraneoplastic neuropathy). So the final diagnosis was metastatic high grade neuroblastoma (stage 4) of unknown primary site. After receiving chemotherapy with cisplatin, doxorubicin, and etoposide and with supportive managements, his general health improved and the

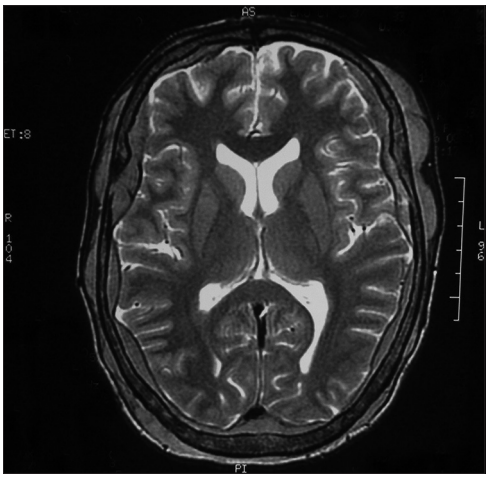

Figure 1: Magnetic resonance imaging brain showed irregular soft tissue swellings both outside and inside skull

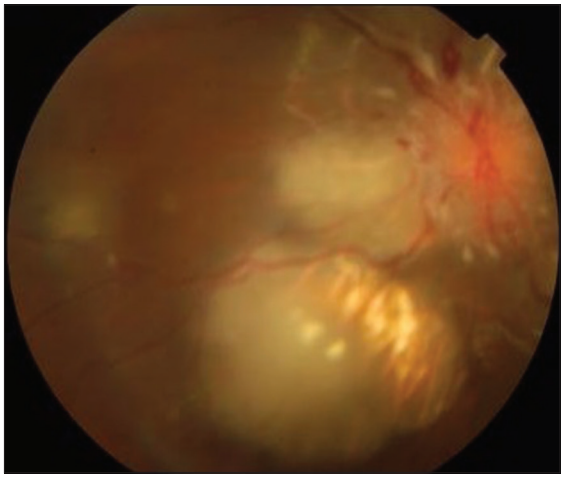

Figure 2: Fundoscopy revealing choroidal metastatic deposits with retinal edema and exudates; also papilledema and retinal hemorrhage

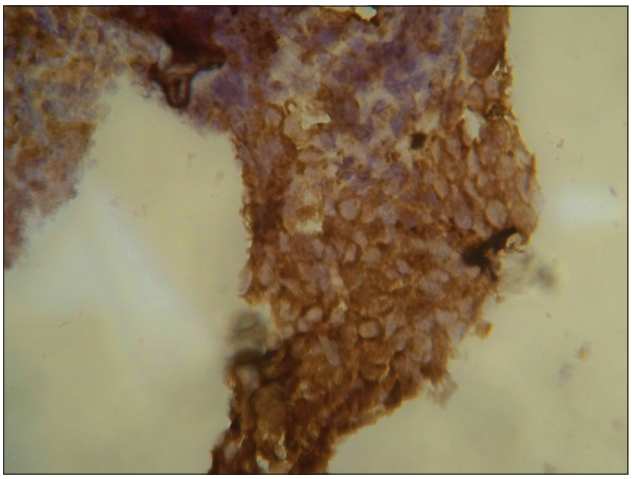

Figure 3: Histopathology of biopsy from scalp mass showing small round cells with scanty cytoplasm and positivity for neuron-specific enolase

swellings reduced. But his visual acuity remained poor. Anemia, high ESR, LDH, and uric acid levels were corrected automatically. Follow-up MRI scan showed no trace of the previous soft tissue swellings.

DISCUSSION

Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy. But only 10% of cases occur in people older than 5 years of age and less than 2% cases were over 18-year-old.[5,6] In our case, the patient's age was 18 years which is quite rare.

The most common primary site of origin is the adrenal glands (in 40% of localized and 60% of widespread disease). Neuroblastoma can also develop anywhere along the sympathetic nervous system chain. Frequencies in different locations include: Neck (1%), chest (19%), abdomen (30% non-adrenal), and pelvis (1%). In rare cases, no primary tumor can be discerned.[7] In our case no primary tumor was found.

The first symptoms of neuroblastoma are often vague, making diagnosis difficult. Fatigue, loss of appetite, fever, and joint pain are common. Symptoms depend on primary tumor locations and metastasis, if present. A tumor can present with a lump, with dyspnea or compressive myelopathy according to the location. Bone lesions in the legs and hips may cause pain and limping. Marrow infiltration may cause anemia. Sometimes they present with paraneoplastic manifestations. In our case the patient at first developed only some vague symptoms, for example, fever, generalized weakness, anorexia, and weight loss. So in any patient of prolonged undiagnosed fever, possibility of a malignancy like neuroblastoma should be kept in mind. Fifty to 60% of all neuroblastoma cases present with metastases only. Metastases are present in up to 70% of patients with neuroblastoma at the time of diagnosis. Most common metastatic sites are bone, local lymph node, liver, intracranial, and pulmonary.[1] Skeletal metastases occur in up to 60% of cases with a variable radiological appearance (ranging from erosion to pathological fracture).[1] In our case there was erosive lesion over left scapula. There were few lytic lesions on skull evidenced by MRI. But no other bony abnormality was found on imaging of thorax, abdomen, and other long bones.

Secondary craniocerebral neuroblastoma manifests most often as osseous metastasis involving the calvaria, orbit, or skull base. Central nervous system (CNS) metastases are usually from tumor infiltration of the mesoderm (dura) and neural crest (leptomeninges).[8] Dural metastases are almost always associated with osseous metastases and can be hemorrhagic. In our case, there were lytic lesions on skull and soft tissue swellings involving scalp. Soft tissue masses inside the skull bone were suggestive of cranial dural involvement. There was no brain parenchymal involvement. There was also bone marrow involvement associated with severe anemia.

Eye manifestations in neuroblastoma may be exophthalmos, periorbital ecchymoses (raccoon eyes), palpable masses, edema of conjunctiva, papilledema, strabismus, anisocoria, or opsoclonus.[9] In our case ocular involvement was in form of choroidal metastases. It is known that most common location in the eye for metastases is the choroid. Most common cancer metastatic to the eye in males is lung cancer and in females is breast cancer and in children is neuroblastoma.[2-4] There are case reports describing choroidal metastasis of neuroblastoma in children. But we could not find the same in adults even after extensive search of available literatures. In this aspect our case is unique.

Paraneoplastic syndromes associated with neuroblastoma may be sweating, flushing, pallor, headache, palpitation, dehydration, hypokalemia and abdominal distension, secretory diarrhea, failure to thrive, opsoclonus, myoclonus, etc.[9] In our case there were findings suggestive of paraneoplastic peripheral neuropathy as no other apparent cause of neuropathy was found.

Neuroblastoma is usually diagnosed by imaging studies (CT scan/MRI). Metaiodobenzylguanidine (MIBG) or PET scan may be required to further evaluate and stage the disease. In our case a diagnosis of metastatic stage-4 disease was already done by CT scan and MRI. Furthermore, the patient could not afford MIBG/PET scan. So without waiting for further imaging treatment was started.

On microscopy, the tumor cells are typically described as small, round, and blue. Rosette patterns (Homer-Wright pseudorosettes) may be seen. Although a number of antigens can be found on neuroblastomas, NSE is the most sensitive. Others are neurofilament protein, S-100, chromogranin, synaptophysin, vasointestinal peptide, etc., In our case the positivity for NSE and synaptophysin confirmed the diagnosis.

In about 90% of cases of neuroblastoma, elevated levels of catecholamines or their metabolites (e.g., dopamine, homovanillic acid (HVA), and/or vanillylmandelic acid) are found in urine or blood. In our case these tests were not done because the diagnosis was already made.

The treatment options for high-risk neuroblastoma are intensive chemotherapy, surgery, radiation therapy, bone marrow/hematopoietic stem cell transplantation, biological-based therapy with 13-cis-retinoic

acid (isotretinoin), and antibody therapy usually with the cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-2.[10] In our case the patient was treated with combination chemotherapy and he responded well to treatment.

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