NEUROBLASTOMA IN THORACIC REGION IN ADULTS : A REPORT OF FIVE CASES

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Over the last two years we diagnosed five adults to have neuroblastoma. The mean age was 21 years and duration of symptoms four months. All patients had bulky disease localized to the thoracic region. Histologically the appearance was that of malignant round cell tumor and superficially the patients appeared to have non-Hodgkin lymphoma. We carried out detailed staging procedures including computed tomography (CT) scans of the chest, abdomen and pelvis, bone marrow aspiration and biopsy, immunohistochemistry and catecholamine estimation to arrive at a diagnosis of neuroblastoma in all patients. As this tumor is extremely rare in adults, its biological behavior is largely unknown. None of the patients was curable, possibly due to bulky disease and the age of the patients. Only palliation and/or prolongation of survival could be achieved.

Neuroblastoma is one of the malignant round cell tumors (MRCT), the others being Ewing sarcoma, rhabdomyosarcoma and non-Hodgkin lymphoma (NHL). Approximately 50% of cases of neuroblastoma occur during the first two years of life and 66% under the age of five years.[1] The Third National Cancer Survey in the United States from 1969 to 1971 found an annual incidence of neuroblastoma to be seven million African Americans and 9-1/2 million Caucasians.[2] It is extremely rare above the age of 12 years. Until 1986, only 42 adult patients had been reported.[3] Of all sites, the abdomen has been reported to be the site of origin in 75% of the cases. The thoracic region is an uncommon site, accounting for only about 25% of cases.[4] We hereby report five adult cases of MRCT in the thoracic region that, on investigation, were found to be neuroblastomas.

Case Reports

Case 1:

A 15-year-old male presented with pain in the upper part of the left side of the chest of seven months' duration and a two month history of anorexia and weight loss. A CT scan revealed a 7 cm x 9 cm opacity with some calcification in the left upper zone adjacent to the dorsal vertebrae. A Trucut biopsy of the mass revealed MRCT suggestive of neuroblastoma. A 24-hour urinary vanillylmandelic (VMA) estimation was normal. Pentavalent technetium 99m dimercaptosuccinic acid (DMSA) scintigraphy demonstrated avid concentration in the region. Surgical opinion was obtained and surgery was considered risky because of proximity of tumor to vessels. The patient declined chemotherapy and was treated with radiotherapy. A dose of 30 Gy was given to the tumor region over 10 fractions and this resulted in temporary palliation of pain and dyspnea. The patient was from Nepal and returned to his home town where he died two months later.

Case 2:

An 18-year-old female presented with pain in the left side of the chest of two months' duration. There was a firm swelling fixed to the fourth rib in the infra-axillary region. A CT scan showed a mass 8 cm x 11 cm in size with intra- and extrathoracic component along the fourth rib, causing its partial destruction. Twenty-four hour urinary VMA was 35.5 µg (normal 2 µg to 8 µg). An ultrasound guided biopsy of the mass revealed MRCT. Pentavalent technetium 99m DMSA scintigraphy demonstrated avid uptake of this marker along the fourth rib and in the mass. The patient was given dose intensive cyclophosphamide chemotherapy.[5] This consisted of cyclophosphamide 140 mg/kg over two days, doxorubicin 25 mg/m^2/day over three days, vincristine 0.05 mg/kg/day on days one, two, and nine followed by three courses of three weekly doses of cisplatin 40 mg/m^2/day and VP-16 150 mg/m^2/day, both for three days. Four such courses were given as soon as the granulocyte count was 1500/dL. The patient achieved partial remission. This was followed by surgical resection of the residual mass lesion along with the rib and adjacent parietal pleura. The histology of the mass showed round cell tumor compatible with neuroblastoma. The patient was thereafter subjected to radiotherapy. A dose of 50 Gy over 25 fractions was given over a large area where the tumor was originally located. The patient developed progressive

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disease towards the end of radiotherapy in the form of pleural effusion and died.

Case 3:

A 21-year-old male presented with nonproductive cough and progressive difficulty in breathing of two months' duration. This was associated with weight loss and anorexia. The patient was emaciated and there were signs of pericardial effusion. Chest radiograph revealed enlarged heart shadow in conjunction with an anterosuperior mediastinal mass. An echocardiograph of the heart confirmed a large pericardial effusion. CT scan of the chest essentially confirmed these findings. An ultrasound guided biopsy of the mass showed MRCT. Twenty-four hour urinary VMA estimation was normal. Pericardiocentesis achieved palliation. The family decided against intensive treatment and returned to their country of Nepal where the patient died 20 days later.

Case 4:

An 18-year-old male who had a long history of Stills disease presented with a swelling in the right upper chest and supraclavicular region. A chest radiograph revealed an opacity in the region of the right upper lobe. A CT scan indicated the opacity to be 10 cm x 12 cm in size. It was extending to the mediastinum. Investigations for distant metastasis were negative. Biopsy showed an MRCT. Twenty-four hour urinary VMA was elevated to 24 μg (normal 2 μg to 8 μg). Pentavalent technetium 99m DMSA demonstrated avid concentration of this marker in the region of the mass. The patient was given one course of cyclophosphamide 1 gm/m^2, vincristine 1.4 mg/m^2 and doxorubicin 60 mg/m^2 intravenously, all on day one, but the patient died of progressive disease four days later.

Case 5:

A 35-year-old female presented with a five month history of progressive dysphagia and a two month history of cough and dyspnea. An x-ray of the chest taken two months earlier showed a left paravertebral mass. A CT scan showed a large central chest mass extending to the entire left hemithorax. The mass was extending to the right paravertebral region also and showed speckled calcification (Figure 1). Pentavalent DMSA scan showed an avid uptake. Twenty-four hour urinary VMA was estimated to be 21 μg/L (0 μg to 8 ug). An ultrasound guided Trucut biopsy revealed MRCT suggestive of neuroblastoma. The patient was given the following chemotherapy: doxorubicin 50 mg/m^2, cyclophosphamide 700 mg/m^2 and vincristine 1.4 mg/m^2, all on day one. Four such courses were given at two week intervals. This was followed three weeks later by four courses of VIP chemotherapy. This consisted of cisplatin 20 mg/m^2 on days one through five, ifosfamide 1.2 g/m^2 on days one through five and VP-16 100 mg/m^2 infusion on days one, three and five. This resulted in a partial remission after which surgical resection was recommended. The patient declined this because of the risks involved. In view of this, radiotherapy to the area of residual tumor was started. During the latter part of radiotherapy, the patient developed progressive disease and returned home.

All five patients underwent bone marrow aspiration, biopsy and CT scans of the abdomen and pelvis. None of these tests revealed any involvement. Electron microscopy was not done in any case because neurogenic origin of the tumors was not expected and therefore appropriate samples were not taken. All patients had large lesions that primarily arose in the thoracic region.

Pathology and Histochemistry

All biopsies on routine histology showed malignant round cell neoplasia. Histologically the differential diagnosis was between NHL, Ewing sarcoma and neuroblastoma. All patients showed rosettes on histopathology that are typical of neuroblastoma. Keeping in view the site of the tumors, Ewing sarcoma was unlikely and the close differential was between NHL and neuroblastoma. All patients' tissue samples were subjected to immunohistochemistry. All showed diffuse positivity for neuron-specific enolase (NSE) and negativity for both common leukocyte antigen (CLA) and periodic acid-Schiff (reagent)/(PAS). Care was taken to maintain adequate controls of histochemistry. These tests, in conjunction with the fact that positive immunoreactivity was correlating with negative stains, strongly favored the diagnosis of neuroblastoma.

Discussion

In all our patients, the tumors were thoracic in location and the histologic diagnosis was MRCT. None of the

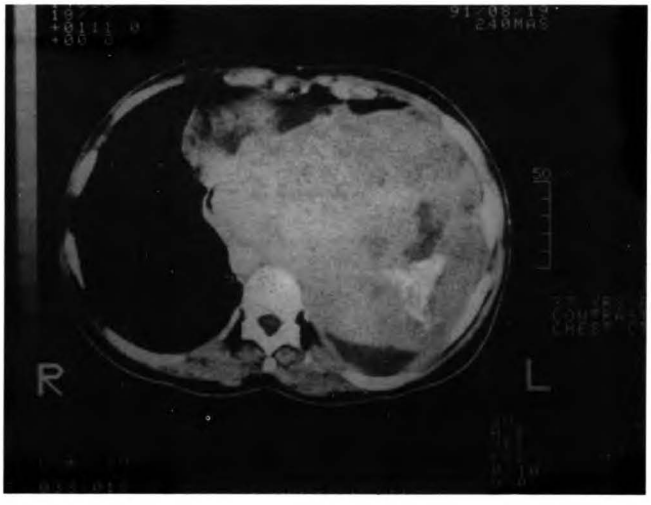

FIGURE 1. Radiograph of chest of case 5 showing the mass with calcification in left hemithorax.

patients had an abdominal mass. Because of this and the age factor, neuroblastoma was not high on the list of differential diagnosis. Clinically the more probable diagnosis was NHL. However, on immunohistochemistry all were repeatedly negative for common leukocyte antigen (CLA), a reliable marker for lymphocytic origin of tumor, and diffusely positive for neuron-specific enolase (NSE), strongly suggesting neuroectodermal origin of the tumor. Tissues were negative for PAS staining, thus eliminating the diagnosis of Ewing sarcoma. Three of the patients also demonstrated elevated levels of VMA in urine. Calcification was seen in the core region of the tumor in three patients, favoring a diagnosis of neuroblastoma. Such calcification is rare in both NHL and Ewing sarcoma. We used a new imaging technique called pentavalent technetium 99m DMSA in four of our patients, all showing an avid uptake. This imaging agent is being currently evaluated at our institute. Our study so far indicates that it could be useful in differentiating neuroblastoma from other MRCT.[6] If this finding is confirmed in a larger study, it could eventually replace meta-iodo-benzyl guanidine (MIBG) which is a rather cumbersome and expensive imaging method currently used in neuroblastoma. In our study, all patients with other round cell tumors such as NHL and soft tissue sarcoma have so far shown negative uptake.

Because of its rarity, the natural history of thoracic neuroblastoma in adults is unknown. Kaye et al. reported six cases in 1986.[7] The mean age was 45 years. In none of their cases was catecholamine estimation reported. The thoracic site represented a mere 20% of all cases. Our five cases of neuroblastoma in the thoracic region seem to be the largest from a single center thus far. The mean age in our series is 21 years and the average duration of symptoms four months before diagnosis was made. There were three male and two female patients. The first published series of cases of neuroblastoma in adults by Mackay et al. suggested that the distribution of the primary disease sites might be different from that in children.[8] They described a series of nine cases where three primary sites were in the head and neck region and three in the lower extremity. Only one patient had primary retroperitoneal disease. Subsequently, neuroblastoma has been shown to occur in the abdomen and thorax in adults as well.[3,9,10] Kaye et al. have reported that the distribution of primary neuroblastoma sites roughly parallels that seen in children.[7] An analysis of adult cases suggests that the growth rate of neuroblastoma in adults may be slower than it is in children, as adults seem to have had symptoms for a longer period of time before diagnosis and many of them seemed to live for three to five years after the diagnosis.[8,9] A total of 85% to 90% of patients with neuroblastoma excrete high levels of catecholamine metabolites.[4] However, Mackay et al. reported these to be elevated in only one of their nine adult cases.[8] Three of our patients demonstrated elevated levels of catecholamines. It is therefore possible that adult patients vary slightly biologically. All of our patients had locally advanced disease at the time of diagnosis. One of the patients was given dose-intensive cyclophosphamide as recommended by Kushner et al. but failed to achieve complete remission.[5] Three patients declined such intensive chemotherapy and one died soon after chemotherapy was started.

Because of the rarity of neuroblastoma in adults, there has been no systematic trial of any combination of chemotherapy regimen. Dosik et al. reported partial responses in three patients older than 18 years with CYVADIC regimen.[11] Kaye et al. noted minor regression of disease in two patients using a combination of cyclophosphamide, dacarbazine and vincristine.[7] This contrasts with the experience of pediatric patients in whom approximately 85% of patients older than one year of age with stage IV disease achieve a good partial response.[12] The apparently slower growth rate of neuroblastoma in adult patients may help to explain the relative resistance to chemotherapy. However, chemotherapy has to be based on current pediatric neuroblastoma regimens until more adult patients are diagnosed and entered into trials.

We recommend that all adult patients with a diagnosis of MRCT should be investigated thoroughly to differentiate the various types and arrive at the correct diagnosis. Investigations should include immunohistochemistry of the tissue, estimation of catecholamines in urine, careful estimation of urinary catecholamines, search for typical radiological calcification, and CT scanning of the whole body to locate the primary site. Furthermore, the place of pentavalent technetium-99 needs to be further investigated, particularly vis-a-vis MIBG scintigraphy in this tumor. Therapeutic trials need to be carried out in a large number of cases to determine the most appropriate treatment, as the biology of this tumor may be different in adults. As this tumor is rare in adults, these results may not be forthcoming in the near future. We wish to emphasize that neuroblastomas, although rare, should be considered in the differential diagnosis of all thoracic masses in adults.

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