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Case report

Intra-abdominal desmoplastic small cell tumors: report of two cases

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Two young adults that presented with intra-abdominal desmoplastic small cell tumors (DSCT) without any evidence of a primary site are described. Both cases share the clinical characteristic features of this rare tumor which include predominant intra-abdominal location as initial presentation, nesting pattern of growth, intense desmoplastic reaction, immunohistochemical reactivity for epithelial, neural and muscle markers, and highly aggressive behavior. Aggressive chemotherapy with a cisplatin-containing regimen was the main therapy to our patients. Up to the present, both cases are alive with disease. The survival is 18 and 15 months from the initial diagnosis, respectively. Interestingly, one of the cases encountered an episode of cerebral infarction at the territory of the left middle cerebral artery 12 days after the first cycle of chemotherapy. This is a previously unrecognized manifestation for this tumor type. This causal relationship between chemotherapy and an acute vascular event is the most likely explanation for our patient's stroke.

Key words: Cerebral infarction, intraabdominal desmoplastic small cell tumor.

Introduction

Intra-abdominal desmoplastic small cell tumor (DSCT) with divergent differentiation is an uncommon malignant neoplasm of childhood and young adults, and was identified as a specific disease entity only a few years ago.[1] This tumor is commonly associated with peritoneal and omental seeding without any evidence of primary lesions in abdominal organs.[2] Histologically, this tumor displays characteristic nests of small cells surrounded by abundant fibromyxoid stroma and expresses divergent differentiation.[1–6] The behavior of this tumor is reported to be extremely aggressive and long-term survival is poor.[7] According to previous reports, this tumor was unresponsive, or transiently responsive, to chemotherapy or radiotherapy.[8] Repetitive aggressive debulking surgery was considered to be the main treatment modality.[3] Herein we report two cases with typical light microscopic and immunohistochemical findings of intra-abdominal DSCT. During the treatment course, one case encountered an episode of cerebral infarct which had not been reported to associate with such tumor. We also discuss the possible mechanisms that may cause the event.

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Case 1

A 29 year old female complained of epigastric fullness and back soreness for 3 months presented in January 1994. On physical examination, a huge deep-seated abdominal mass was palpated. Hematogram showed mild anemia (Hb 10.6 g/dl), mild thrombocytopenia (platelet 141 $\times$ 10^3/ cm^3) with normal leukocyte count (WBC 4300/ cmm^3). Biochemical examinations including lactate dehydrogenase (LDH) were within normal limits. Computerized tomography (CT) scan of the abdomen confirmed the presence of mass lesion at the celiac trunk and para-aortic regions. Microscopic examination of the echo-guided biopsy of the retroperitoneum showed that the tumor was composed of cords and nests of small round cells in a desmoplastic stroma (Figure 1). Immunohistochemical study revealed that the tumor cells were positive for AE1/AE3, desmin and neuron-specific enolase (NSE); but negative for S-100 and common leukocyte antigen (LCA). With the diagnosis of DSCT, we started chemotherapy with cisplatin 30 mg/m^2 and etoposide 100 mg/m^2 for 3 days every 3 weeks for four courses. Re-evaluation by a CT scan of the abdomen showed no reduction of the tumor size.

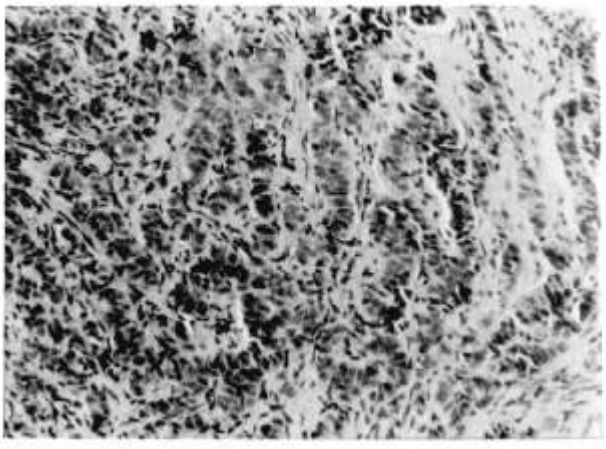


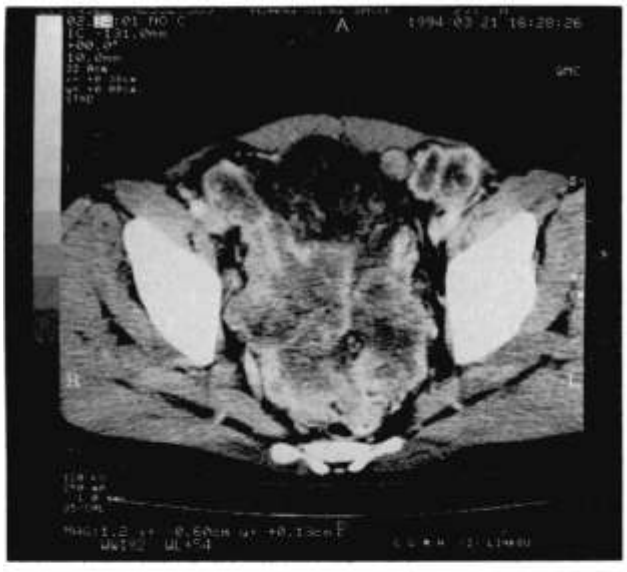
Figure 1. Case 1: high power view of the needle biopsy shows cords and nests of undifferentiated small cells with a fibrous stroma. H&E, ×150.

Subsequent therapeutic effort included local irradiation up to 44 Gy totally. She was followed up closely by chest X-ray. Multiple pulmonary metastases were found 1 year later. This patient is still alive asymptomatically at 18 months after the initial diagnosis.

Case 2

In March 1994, a 27 year old male presented with abdominal distention and complained of small caliber of stool for 1 month. A deep-seated mass around the periumbilical area was discovered on physical examination. Laboratory data revealed normal hematogram and biochemistry except a high LDH value of 327 U/l (normal range 47–140 U/l). α-Fetoprotein (AFP), β-human chorionic gonadotropin (HCG), carcinoembryonic antigen (CEA) and prostate-specific antigen (PSA) screen were non-impressive. A CT scan of the abdomen and pelvic cavity showed multiple heterogeneous soft tissue masses in the abdomen with external compression of the rectum and trigone of bladder also showed the presence of multiple liver nodules (Figure 2). A laparotomy revealed abdominal masses occupying the peritoneum diffusely without apparent primary lesion. Frozen section of the soft tissue was demonstrated to be desmoplastic small round cells (Figure 3). No gross peritoneal tumor tissue was resected. Immunohistochemical study revealed that the tumor cells were positive for AE1/AE3, epithelial membrane antigen (EMA), chromogranin A, NSE and vimentin, but negative for LCA and desmin.

This patient was placed on a chemotherapy regimen used for germ cell tumor (PVB cisplatin, etoposide and bleomycin).[9,19] An episode of stroke with



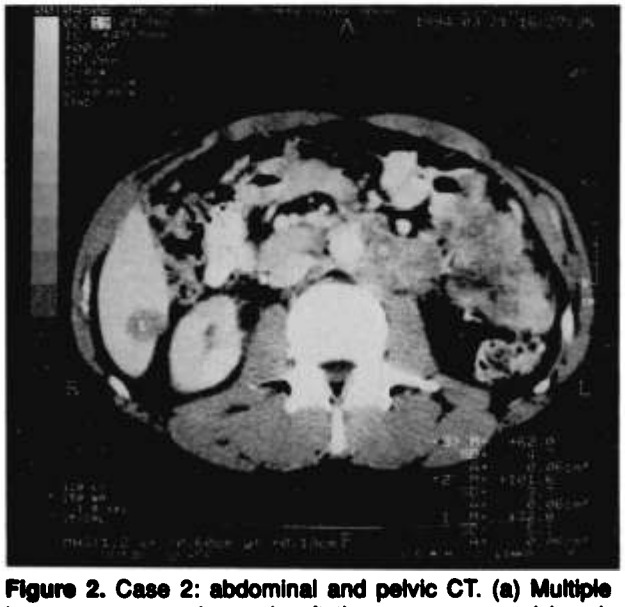


Figure 2. Case 2: abdominal and pelvic CT. (a) Multiple heterogeneous enhanced soft tissue masses and lymph nodes metastases in the pelvic cavity. External compression of the rectum and trigone of the bladder are seen. (b) Masses in left lower and mid-abdomen and lymph node metastases in para-aortic, peripancreatic and hepatoduodenal nodes. Liver metastasis is also noted.

presentation of aphasia, central facial palsy and right limb weakness occurred 12 days after first course of chemotherapy. Immediate CT scan of the brain revealed a low attenuation lesion at the left temporal and frontal lobes with mild mass effect. Ten days later, CT scan and magnetic resonance imaging (MRI) of the brain showed post-infarct hemorrhage in the territory of the left middle cerebral artery (MCA) with no tumor lesion noted. The patient refused angiographic examination. No vege-

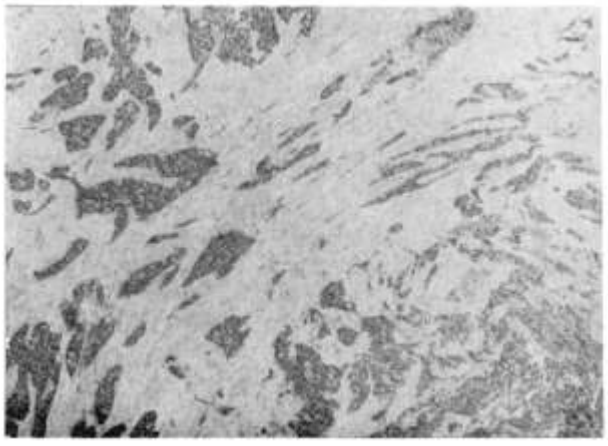


Figure 3. Case 2: low power view shows irregular nests of cords of undifferentiated small cells in a fibrous stroma with marked desmoplastic reaction. H&E, ×30.

tation was found by two-dimensional echocardiogram and non-invasive carotid doppler sonography. A coagulation profile showed no evidence of coagulopathy. A blood culture grew no microorganisms. Given supportive care, this patient recovered from the stroke gradually and there was no apparent evidence of disease progression. We restarted the same chemotherapy regimen 1 month later and partial remission was achieved after five courses of PVB therapy. The patient refused the suggestion of a second exploratory laparotomy with debulking surgery. The tumor regrew recently; however, his disease is always confined to the abdomen. The patient is still alive 16 months after the initial diagnosis. Now he is on supportive care. A follow-up CT scan of the brain 6 months after his stroke showed a small residual low attenuation lesion.

Discussion

Intr-abdominal DSCT is a rare malignant neoplasm of childhood and young adult with a predilection for males.[7] The disease entity was first identified by Gerald and Rosai in 1989.[1] Besides the specific microscopic finding of an intensive desmoplastic reaction between the nesting pattern of small cells growth,[11] the positive activity for epithelial, neural and muscle markers[7,8] is the most important differentiation from the family of neoplasms known as small round cell tumors (SCRT) which includes malignant lymphoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma, rhabdoid tumor, neuroendocrine tumor, primitive neuroepithelial tumor (PNET) and mesothelioma.[3,7,12,13] Both of our reported cases demonstrated similar histological findings with simultaneously triple phenotypical expression, therefore the diagnosis of DSCT is firm although neither electron microscopic ultrastructure nor cytogenetical study were done for further confirmation. The histogenesis of DSCT whether it arises from neurogenic cells, blastoma or mesothelium still remains uncertain.[14–17]

Clinically, this tumor usually displays aggressive courses. According to the report from Gerald *et al.*, of the 17 patients with follow-up information, 15 died as the result of tumor progression, 6 months to 4 years after the diagnosis.[7] Another large series of 22 cases from Ordonez *et al.* also showed a similar result. Sixteen patients died of widespread metastases of their disease 8–50 months (mean, 25 months; median, 25.5 months) from the time of diagnosis and five patients were alive with known metastatic disease.[15] Up to the present time, there was only one case reported by Gonzalez-Crussi *et al.*,[3] claimed to be cured who was free of tumor 4 years after repetitive aggressive laparotomy with resection of the residual tumor, intravenous chemotherapy (adriamycin and cisplatin) and radiotherapy. The other patient also mentioned by Gonzalez-Crussi *et al.* died 6 years after this combined modality treatment. Effective local therapy may have a substantial impact on survival of the patient with this disease. However, the lack of uniformity in approach and the small number of patients in most reports preclude standardization of the treatment of DSCT at present. Although aggressive complete surgical resection of the tumor was still thought to be the mainstay of therapy,[8] the majority of the patients present usually with a huge intra-abdominal tumor mass extending to the omentum, mesentery and peritoneum, where resection of all macroscopic tumors is usually impossible.

A broad spectrum of chemotherapeutic regimens, either single agent or in combination, has been tested in DSCT and usually shown initial partial response followed by uncontrollable tumor relapse. The presence of desmoplastic fibromyxoid stroma may explain the constant chemoresistance of such tumors.[8] Although few complete responses were seen, obvious shrinkage of the abdominal tumor would make complete surgical resection feasible after pre-operative chemotherapy, as proposed by Schmidt *et al.*[4] Our first case did not respond well to chemotherapy of etoposide and cisplatin. Lung metastases developed 1 year after the initial diagnosis; however, the patient is now asymptomatic. The second case achieved partial remission after four courses of chemotherapy of PVB; however, the

patient refused subsequent surgery and the tumor regrew gradually. Both patients are still alive with disease and are on supportive care. Because surgery or chemotherapy alone has shown unsatisfactory results in achieving long-term survivors, an intensive combined-modality approach including preoperative chemotherapy followed by repetitive aggressive laparotomy probably should be advocated. The benefit in terms of survival by using high-dose chemotherapy with autologous bone marrow transplantation or peripheral stem cell support remains to be determined since there was only one reported case in the literature but the patient died of veno-occlusive disease of liver after high-dose chemotherapy.[4]

It was interesting to observe an event of cerebral vascular accident (CVA) in our second case. This is a previously unrecognized manifestation for this tumor type. This episode happened 12 days after initial chemotherapy using the PVB regimen. Immediate CT scan of the brain at the emergency room showed cerebral infarction at the territory of the left middle cerebral artery (MCA). The patient had no signs of sepsis. Coagulation profiles excluded the possibility of chronic disseminated intravascular coagulation (DIC). His two-dimensional echocardiogram revealed a normal left ventricle without evidence of mural thrombus or valvular disease. Non-invasive carotid doppler sonography also showed normal findings. Follow-up CT scan and MRI study of the brain 10 days later showed hemorrhage at the infarction site but there was no evidence of tumor lesion. About 6 months later, a small area of residual low attenuation was still observed by CT scan of the brain. We thought this event encountered in Case 2 was cerebral infarction followed by hemorrhage.

According to the report of Graus *et al.*,[18] half of the CNS disorders found at autopsy in patients with cancer were due to cerebral hemorrhage while the remainder were due to cerebral infarction. Major cerebral infarction in patients with malignant solid tumors is usually secondary to a hypercoaguable state or emboli from infectious sites or non-bacterial thrombotic endocarditis (NBTE) as well as atherosclerosis, superior sagittal sinus occlusion and miscellaneous.[19–21] However, the event of this patient seemed difficult to attribute to any one of the above causes. Actually, sporadic case reports of acute cardiovascular events such as myocardial infarction, pulmonary emboli and CVA in young men receiving chemotherapy for testicular cancer have raised concern that these events may be treatment-related complications and impugn the safety of such treatment.[22–24]. It is not well understood whether the pathogenesis of the cerebral infarction is similar to that of the assumed coronary toxicity associated with cisplatin and bleomycin.[25] Despite the fact that the retrospective study by Nicholas *et al.*[26] reported no evidence of acute cardiovascular complications associated with chemotherapy for testicular cancer, we still suspect that this causal relationship between chemotherapy of PVB and the acute vascular event is the most likely explanation for our patient's CVA event.

DSCT is a rare and new disease entity. These data are difficult to compare with data from the previous literature because the treatments for DSCT have not been standardized; there are insufficient results to give any conclusion. Our purpose here is to bring the clinical and histological features of the tumor to general attention since they still represent a challenge for clinicians and surgeons who are not familiar with the specific tumor type. We also would like to suggest that in patients treated on a chemotherapy regimen used for testicular cancer, special attention should be paid to symptoms suggestive of acute cardiovascular or cerebrovascular events.

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