Peripheral nerve entrapment: An unusual adverse event with high-dose interleukin-2 therapy

Recombinant interleukin 2 (rIL-2) is a promising biological therapy agent in the treatment of patients with metastatic renal cell carcinoma and metastatic melanoma [1, 2]. The antitumor effects are a result of a complex interplay of generation of NK and T-cells and secretion of a variety of lymphokines (IFN, IL6 and TNF) [3]. Early studies and success with rIL-2 were reported with the high dose intravenous bolus administration regimen [4–6].

High dose rIL-2 therapy is associated with significant morbidity [7], which is primarily related to the vascular leak syndrome (VLS) [8] and effects all the major organ systems; predominantly the cardiovascular, renal, gastrointestinal, hemato logical and central nervous system. Neurological involvement is usually in the form of restlessness, confusion, disorientation and rarely convulsions [7]. Peripheral nervous system involvement is uncommon, and has been previously reported to present as a nerve entrapment syndrome [9]. We have observed the same adverse event with two of our patients undergoing rIL-2 therapy for renal cell carcinoma and malignant melanoma.

Patient 1

A 70-year-old white male who presented with a locally advanced of renal cell carcinoma with metastases to the left supraclavicular lymph node. Associated medical disorders included benign ventricular ectopy and type II diabetes mellitus. The patient underwent three courses of high dose IL-2 therapy; wherein he received 13 and 9, 9 and 5, and 5 and 6 doses, respectively, in cycles 1 and 2 of each course. Adverse events during the course of his therapy included: weight gain of 10–15 kg during each course of treatment; periods of mental confusion, agitation, and drowsiness; and episodic deformity. Therapy was stopped due to the rapid weight gain, predominantly in the upper extremity, with severe pain in both hands though without any sensory or motor deficit on examination. Follow-up EMG confirmed the diagnosis of bilateral median mononeuropathies at or distal to the wrist.

Patient 2

A 53-year-old white female with metastatic melanoma from a vulvar primary was placed on the high dose IL-2 therapy. The first course consisted of 14 and 10 doses; a second course included 8 and 10 doses. Adverse effects included the following: weight gain of 15 kg per course; electrolyte abnormalities and hypotension. During her last course, she complained of a tingling sensation and pain in her right hand which was diagnosed as Carpal Tunnel Syndrome (CTS). She did not report any sensory deficit and her symptoms improved with the use of a wrist splint. During follow-up, she had partial response to IL-2 therapy and thus was treated with her third course of IL-2 therapy. In view of her prior history of CTS, she was treated on a regimen of fluid restriction with early institution of neosynephrine infusion to manage hypotension and to minimize fluid retention and thus successfully avoided a recurrence of CTS.

The accumulation of fluid in soft tissues of extremities, secondary to VLS may well be responsible for the CTS observed in these patients. The time course of the adverse event, documented peripheral edema and substantial weight gain substantiates the hypothesis of the compression median neuropathy which was documented clinically and by neurophysiological studies. Early recognition and conservative therapy along with adequate correction of the offending factor resulted in the complete recovery in both the patients and even allowed us to administer another course of treatment, with careful fluid management and vasopressors, in one of the patients.

Diabetes mellitus, rheumatoid arthritis, local trauma with deformity etc. predisposes to CTS and may thus be precipitated in the context of IL 2 therapy. Other nerve entrapment syndromes such as tarsal tunnel syndrome (entrapment of the posterior tibial nerve beneath the lancinate ligament) and the ulnar nerve entrapment behind the medial epicondyle may also manifest as an adverse event following IL 2 therapy. Peripheral nerve entrapment syndromes during IL 2 therapy should be seriously considered in an appropriate clinical situation, especially as early recognition and appropriate therapy may limit many long term disability.

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References

Intra-abdominal abscess and
tumor-enteric fistula formation: An unusual complication of chemotherapy for advanced testicular choriocarcinoma

Rapid tumor lysis following intensive chemotherapy for metastatic or locally advanced tumors has been described as resulting in spontaneous malignant pneumothorax and gastric or bowel perforation. Bowel wall involvement by tumors may lead to necrosis and, eventually, to perforative sequelae such as intra-abdominal abscess formation, clearly visualized on CT scan and/or by ultrasonography [1-3]. Primary contributing factors are drug-induced immunocompromised states, such as neutropenia-induced infection and local ischemic events due to obstructive edema and drug-induced ileus (vincristine). The resultant bowel stasis may lead to bacterial overgrowth at sites of denuded and damaged mucosa [4].

Germ cell malignancies are highly chemosensitive. Following cisplatin-based chemotherapy for bulky retroperitoneal masses, primary complete remission can be obtained in 60%-80% of patients while in another 10%-15%, disease-free status can be achieved by surgical removal of the residual tumor [5]. We describe an unusual case of intra-abdominal infection following chemotherapy for advanced testicular carcinoma.

A 24-year-old male patient was referred to the Oncology Department of the Rambam Medical Center following left inguinal orchiectomy. Histology demonstrated pure choriocarcinoma. Physical examination revealed a huge left abdominal mass. CT scan and ultrasound showed a bulky retroperitoneal mass encasing the aorta, and moderate left hydro-nephrosis. Chest X-ray and CT scan were consistent with multiple bilateral lung metastases (maximal diameter 1 cm). The β-subunit of human chorionic gonadotrophin (β-HCG) was 292,000 units, and α-fetoprotein level was within normal range.

The standard BEP regimen (bleomycin, VP-16, cisplatin) was initiated. Following two full-dose BEP cycles, a good partial remission was noted. The β-HCG levels dropped rapidly (62 units). On day 11 of the second BEP cycle the patient became febrile (up to 39 °C), without neutropenia or any evidence of infection. His general condition was good. Results of a repeat abdominal CT scan were consistent with a huge polycyclic, necrotic tumor mass in the left abdomen (Figure 1). As the fever did not resolve, fine needle aspiration was performed under CT guidance, yielding serous fluid positive for Escherichia coli.

The patient was started on broad spectrum antibiotics and a CT-guided drain was inserted into foci of apparent abscess, yielding mixed bacteriological culture, positive for gram-negative and gram-positive bacilli and gram-positive cocci.

Due to the unresolved fever and persistence of the intra-abdominal infection, the patient underwent surgical removal of the necrotic and infected retroperitoneal masses, including adherent small bowel loops, because of an existing fistula between the loops and the tumor mass. An attempt was made to resect all residual tumor masses, but optimal debulking could not be achieved. Histological specimens of the intestinal wall, including the fistulous area, revealed necrosis, inflammation and infiltration by malignant trophoblasts (Figure 2).

The level of β-HCG was still high following surgery (103 units), indicating persistent disease. A second-line regimen consisting of ifosfamide (with Mesna), etoposide (VP-16) and cisplatin was introduced. On this protocol, tumor markers returned to normal, as did results of the chest CT. The remaining retroperitoneal masses disappeared almost completely.

The patient underwent re-resection of the residual retroperitoneal masses, which proved to be fibrosis alone, without evidence of persistent infection. He is currently being followed, with no evidence of disease or disabling side effects.

Our patient exhibited an extremely rare instance of intra-