Weakness and numbness after chemotherapy for metastatic non-seminoma testis: A new neurological complication

ROBERT C. VERDONK[1], ROELIEN H. ENTING[2], MIRJAM JANMAAT[2], CAROLINE P. SCHRODER[1], DIRK Th. SLEIJFER[1] & JOURIK A. GIETEMA[1]

[1]*Department of Internal Medicine, Division of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands and* [2]*Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands*

To the Editor

Germ cell tumors have been associated with paraneoplastic neurological syndromes, mainly encephalitis, and its treatment with peripheral neuropathy. We present a 41-year-old male treated with chemotherapy for a germ cell tumor who developed a Guillain-Barré syndrome, an acute demyelinating neuropathy. This is the first case of Guillain-Barré potentially related to a germ cell tumor described in the literature to date.

Case presentation

A 41-year-old man of Arabic descent was admitted to the Department of Medical Oncology. Physical examination at another hospital had revealed a tumor of the left testis, and a supraclavicular mass. An inguinal orchidectomy was performed and pathological examination showed embryonal cell carcinoma and diffuse embryoma. Further work-up revealed a stage IV non-seminoma of the left testis with a good risk according to the IGCCG [1]. The patient was referred to our hospital for chemotherapy. Two months before the current admission three courses of BEP chemotherapy (Bleomycin 30 mg/day on day 2,8 and 15, Etoposide 100 mg/m^2 on day 1–5 and Cisplatin 20 mg/m^2 on day 1–5) were given at an interval of 3 weeks, without any substantial toxicity, besides some symptoms of coughing after the last course.

One week after the last dose of Bleomycin of the third cycle the patient was seen at the outpatient clinic because of fatigue, generalized weakness and numbness in the feet and hands. Laboratory investigation was unremarkable with normal tumor markers, blood count, electrolytes, kidney and liver function. Examination by a neurologist revealed normal cranial nerve function and no weakness of his arm muscles. There was an inconsistent weakness of the iliopsoas, quadriceps and hamstrings grade 4 of 5 on the MRC-scale (Medical Research Council). Achilles tendon reflexes were absent. There was a subtle decrease in vital sensibility of the peripheral limbs. Diagnosis at that time was a cisplatin-induced polyneuropathy with aggravation. No specific treatment was given. Two days later the patient was admitted with progression of malaise, dyspnea, weakness and difficult micturition. Cardiopulmonary examination, chest x-ray, electrocardiogram and extensive laboratory studies did not reveal any abnormalities. Neurological examination was repeated, and now showed a paresis grade 4 of the hand muscles and a progressive paresis of the legs: proximal strength 2/5, distal 4/5. All tendon reflexes were abolished. Hypoesthesia was present in the proximal limbs. Straight leg raising was very painful. The differential diagnoses were infectious polyradiculoneuropathy, leptomeningeal metastases, Guillain-Barré syndrome or a paraneoplastic phenomenon. The clinical picture was too severe for chemotherapy-induced polyneuropathy. MRI of the total spine was normal. Analysis of the spinal fluid showed an a-cellular fluid with markedly increased protein content: 2.8 g/l (Normal <0.5 g/l). Malignant cells were not seen. Nerve conduction studies showed normal motor conduction velocities but a conduction block in the ulnar nerve. Dispersal of the compound muscle action potential (CMAP) was seen in multiple nerves. Sensory nerve conduction velocities were slightly reduced in the arms, and sensory nerve action potential (SNAP) were absent in the superficial peroneal nerves. Lower extremity F-waves were absent. Needle electrode examination showed normal motor unit potential number and reduced recruitment in both examined

Correspondence: Robert C. Verdonk, University Medical Center Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, the Netherlands. Tel: +31 50 3616161. E-mail: r.c.verdonk@int.umcg.nl

(Received 7 December 2007; accepted 18 December 2007)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860701877330

leg muscles. These changes are consistent with early Guillain-Barré syndrome [2].

At that time the diagnosis of Guillain-Barré syndrome was made. The patient was treated at the department of Neurology with intravenous immunoglobulins. Analysis for specific antibodies associated with paraneoplastic syndromes (anti-Hu, Yo, Ri, Tr, Amphysine, CV2, Ma2) tested negative. The clinical course was that of a slow but gradual improvement without any respiratory failure.

Discussion

The present report is first in the literature suggesting a relationship between a germ cell tumor during chemotherapy treatment and Guillain-Barré syndrome.

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating neuropathy characterized by acute onset of peripheral and cranial nerve dysfunction. It can present with both sensory and motor disturbances. The incidence is 1.2–1.9 per 100 000 in Europe [3]. Although pathogenesis is incompletely understood, most likely there is a humoral and cellular immune-reaction aimed at the myelin or the axon of peripheral nerves. Molecular mimicry after a previous bacterial of viral infection is probably an important precipitating factor, with a previous *Campylobacter jejuni*-infection most commonly mentioned [3]. Patients present with pain, numbness and weakness in the limbs. Facial and respiratory nerves can be involved leading to respiratory insufficiency in up to 25% of cases. Treatment is with intravenous immunoglobulins or plasmapheresis.

Paraneoplastic neurologic syndromes are a heterogeneous group of neurologic disorders. In some cases a relationship with a specific antibody can be established, a so-called anti-onconeural antibody [4].

Germ cell tumors have been associated with these syndromes, especially encephalitis. In most cases this encephalitis is related to anti-Ma2-antibodies [5].

Neurological symptoms can also occur due to anti-cancer treatment. Chemotherapy-induced polyneuropathy has been shown to occur in up to 29% of patients undergoing BEP-chemotherapy [6]. Cisplatin may cause an axonal, predominantly sensory polyneuropathy [7].

GBS has also been associated with malignancies. Patients experiencing this syndrome have an odds-ratio of 2.4 of suffering from a malignancy compared to the general population [8]. No specific antibody has been identified to date. GBS associated with lung cancer, lymphoma, esophageal cancer and other solid organ malignancies have been reported [8].

A number of pathogenic factors may have played a role in the development of GBS in this particular patient. Although the co-occurrence can be mere chance, we feel there is an actual relationship between the tumor, its treatment and the GBS. First, it could be related to the germ cell tumor as a 'genuine' paraneoplastic syndrome. The short interval between the diagnosis of non-seminoma and GBS are strongly suggestive for this explanation [4]. Secondly, the GBS could be related to the chemotherapeutical treatment. GBS occurring during or shortly after treatment with platinum-containing compounds has been described in patients with cancer of the endometrium, lung or colon [9,10]. The pathogenesis could involve increased amounts of circulating tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) known to occur during treatment with these compounds [9,10]. IL-6 and TNF-α are elevated in patients with active GBS. A third possible mechanism is the immunosuppressed state during chemotherapy. A generalized immuno-depressed state may lead to loss of immuno-regulatory mechanisms, predisposing to the inflammation known to occur with GBS [3]. Finally, the symptoms of a potential respiratory infection after the last course of BEP could be involved. This however seems less probable considering the short interval between coughing symptoms and first manifestation of GBS (<5 days) and the absence of fever, inflammatory parameters and x-ray abnormalities.

In conclusion, we present the first case of Guillain-Barré syndrome associated with chemotherapy treatment for a germ cell tumor. Potential pathogenic factors are tumor-induced antibodies against myelin, use of cisplatinum or a generalized immunosuppressed state.

References

[1] International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: A prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15:594–603.

[2] Gordon PH, Wilbourn AJ. Early electrodiagnostic findings in Guillain-Barre Syndrome. Arch Neurol 2001;58:913–7.

[3] Hughes RA, Cornblath DR. Guillain-Barre syndrome. Lancet 2005;366:1653–66.

[4] Antoine J-C, Mosnier J-F, Absi L, Convers P, Honnorat J, Michel D. Carcinoma associated paraneoplastic peripheral neuropathies in patients with and without anti-onconeural antibodies. J Neurol Neurosurg Psychiatry 1999;76:7–14.

[5] Voltz R, Gultekin SH, Rosenfeld MR, Gerstner E, Eichen J, Posner JB, et al. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. NEJM 1999;340:1788–95.

[6] de Wit R, Stoter G, Kaye SB, Sleijfer DT, Jones WG, ten Bokkel Huinink WW, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: A randomized study of the European Orga-

nization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol 1997; 15:1837–43.

[7] Krarup-Hansen A, Helweg-Larsen S, Schmalbruch H, Rorth M, Krarup-C. Neuronal involvement in cisplatin neuropathy: Prospective clinical and neurophysiological studies. Brain 2007;130:1076–88.

[8] Vigliani MC, Magistrello M, Polo P, Mutani R, Chio A. Risk of cancer in patients with Guillain-Barré syndrome (GBS). A population-based study. J Neurol 2004;251:321–6.

[9] Tho LM, O'Leary CP, Horrocks I, Al-Ani A, Reeds NS. Guillain-Barre syndrome occurring after adjuvant chemoradiotherapy for endometrial cancer. Gynecol Oncol 2006; 100:615–7.

[10] Christodoulou C, Anastasopoulos D, Visvikis A, Mellan S, Detski I, Tsiakalos G, et al. Guillain-Barré syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy. Anti-Cancer Drugs 2004;15:997–9.

Real-time PCR quantification of human DKC1 expression in colorectal cancer

MIMMO TURANO[1], ALBERTO ANGRISANI[1], MARINA DE ROSA[2], PAOLA IZZO[2] & MARIA FURIA[1]

[1]*Dipartimento di Biologia Strutturale e Funzionale, Università di Napoli "Federico II", via Cinthia, 80126 Naples, Italy,* [2]*Dipartimento di Biochimica e Biotecnologie Mediche, Università di Napoli Federico II, via S. Pansini 5, 80131 Naples, Italy*

To the Editor

Mutations in the highly conserved human DKC1 gene cause the rare genetic disease X-linked recessive dyskeratosis congenita (X-DC) [1]. X-DC patients display features of premature aging, mucosal leukoplakia, nail dystrophy, skin pigmentation, interstitial fibrosis of the lung, bone-marrow failure and increased susceptibility to cancer [2]. Hypomorphic DKC1 mutant mice recapitulate the major features of X-DC, including increased cancer susceptibility. These mice were in fact highly prone to tumors and developed a variety of them, most commonly from lung and mammary gland, indicating that DKC1 may act as an important tumor-suppressor *in vivo* [3]. DKC1 encodes a nucleolar protein, named dyskerin, which acts as pseudouridine synthase and constitutes one of the four core protein components of the specific H/ACA RNPs involved in RNA pseudouridylation [1]. Dyskerin proved to be essential also for proper rRNA processing, thus playing multiple roles on ribosome biogenesis [3]. Moreover, this protein has been recently identified as an essential component of the catalytically active human telomerase complex, together with the human telomerase reverse trascriptase (TERT) and the RNA component of telomerase (TERC) [4]. A quantitative analysis of dyskerin mRNA expression was recently performed by real-time RT-PCR on a series of breast carcinomas [5]. In this study, the TERC levels and the overall degree of rRNA pseudouridylation were also evaluated. The amount of dyskerin mRNA was found to be variable, but always significantly associated with TERC and rRNA pseudouridylation levels.

Considering that dyskerin and TERT are both constituents of the active human telomerase enzyme complex [4] and that TERT has been indicated as a potential biomarker for colorectal cancer [6], we wished to check whether dyskerin and TERT mRNA levels would vary in parallel in colorectal tumors. According to the multiple role played by dyskerin in ribosome biogenesis, its expression levels were expected to be highly variable in different patients, possibly depending on age, sex and general metabolic conditions. To take in account this aspect, in our experiments we always referred as control to adjacent non-tumor mucosa matched samples.

Normal colorectal mucosa and colorectal cancer tissues were then sampled from 8 patients affected by sporadic colon cancer and assayed by quantitative real-time RT-PCR analysis. Institutional ethical approval and informed consent were given by the patients undergoing surgery for colorectal cancer. Total RNA was extracted purified and reverse-

Correspondence: Mimmo Turano, Dipartimento di Biologia Strutturale e Funzionale, Complesso Universitario di Monte S. Angelo, Università di Napoli Federico II, Via Cinthia 80126 Naples, Italy. Tel: +39 081 679076. Fax: +39 081 679300. E-mail: mimmo.turano@unina.it

(Received 11 December 2007; accepted 7 January 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860801898616