Romiplostim reverts the thrombocytopenia in dengue hemorrhagic fever

To the Editor: First-generation thrombopoietic agents were recombinant forms of human thrombopoietin (TPO), but their development was discontinued due to the onset of neutralizing auto-antibodies cross-reacting with endogenous TPO. Second-generation thrombopoiesis-stimulating molecules (romiplostim and eltrombopag), have completed phase III trials in primary immune thrombocytopenia, whereas phase II and III trials are ongoing in other conditions characterized by thrombocytopenia.1 Dengue is the most prevalent arthropod-borne virus affecting humans today causing a spectrum of disease, ranging from a mild febrile illness to a life-threatening dengue hemorrhagic fever (DHF).2 The main hematological findings of dengue are leukopenia, thrombocytopenia, lymphocytopenia and the presence of atypical lymphocytes; in DHF, the thrombocytopenia is more prolonged, while the other hematological abnormalities are not.3 DHF is endemic in México.4,5

Multiple myeloma was identified in November 2007 in a 54-year-old woman; she was initially treated with thalidomide/dexamethasone/bortezomib until achieving a very good partial response and then autografted using high-dose melphalan.6 After the autograft, she was given thalidomide, 100 mg/day. Thirty-six months later she developed headache, gastrointestinal symptoms, retro-orbital pain, myalgia, joint pain, petechiae, purpura and gum bleeding. The blood cell count disclosed thrombocytopenia (2×10^9/L), leukopenia (0.7×10^9/L) and granulocytopenia (0.05×10^9/L); dengue virus antigens and IgM antibodies were present; the bone marrow had hypoplasia and no evidence of myeloma was found. The patient was treated with intravenous hydrocortisone (300 mg/day) and subcutaneous filgrastim (300 µg/day), with the neutropenia resolving 4 days later. The thrombocytopenia did not resolve and was later treated unsuccessfully with oprelvekin and platelet transfusions. Fifty-two days after the thrombocytopenia ensued, subcutaneous romiplostim (4 µg/Kg/week) was started, and the platelet count increased promptly (Figure 1). The patient remained with >100×10^9/L platelets, 230 days after starting romiplostim.

Treatment of dengue fever, whether in its uncomplicated form or with hemorrhagic manifestations remains symptomatic. Steroids have proved useful when DHF complicates with septic shock7 and even though thrombocytopenia resolves spontaneously frequently, may be prolonged in certain circumstances.8 There are reports of anti-D immune globulin in DHF cases with severe and prolonged thrombocytopenia6 but to the best of our knowledge, this is the first case of DHF in which romiplostim has been successfully used. An immune mechanism of thrombocytopenia due to increased platelet destruction appears to be operative in patients with DHF;9 however, in the case that we are reporting, the previous stem cell transplant and the use of thalidomide led to a hypoplastic marrow which most likely was unable to compensate the peripheral platelet destruction.

Romiplostim has been shown to be effective in ameliorating thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura and other thrombocytopenic conditions.10,11 Its usefulness in this case may stem from the combined origin of the thrombocytopenia, on one hand the platelet destruction caused by the dengue virus and on the other a hypoplastic marrow derived not only from the viral infection, but also from the previous stem cell allograft and the chronic use of thalidomide.

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Figure 1. Platelet count (x10^9/L) by day. Arrows denote doses of romiplostim (4 µg/kg).

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Platelet count (x10^9/L) by day. Arrows denote doses of romiplostim (4 µg/kg).
Nasal extranodal peripheral NK/T-cell lymphoma treated by the protocol NK/T-cell high-dose-methotrexate L-asparaginase dexamethasone

To the Editor: Extranodal NK/T cell lymphoma, a nasal type lymphoma, is a distinct entity by the WHO classification of lymphomas with a frequency of less than 1% of all non-Hodgkin lymphoma (NHL) in the West and the North Africa and an increased incidence in Asia. Standard treatment is not well established and anthracycline containing combination chemotherapy (CHOP) had less than 30% survival at 5 years in localized disease. We report a case of extranodal NK/T cell lymphoma, nasal type, treated initially with CHOP as a large cell lymphoma and then with high-dose methotrexate, L-asparaginase and dexamethasone as part of a multicenter phase II clinical trial (GELA-GOELAMS) for extranodal NK/T cell lymphoma.

A 34-year-old man, a welder by profession for 17 years, was seen in September 2008 for a right unilateral nasal obstruction associated with recurrent epistaxis (Figures 1,2). There were no associated B symptoms and performance status was 1. Anterior rhinoscopy revealed a right nasal cavity ulcerated mass with bleeding on touch. There was no other abnormal finding on physical examination with no peripheral adenopathy or hepatosplenomegaly. The diagnosis of NHL was established after several attempts at biopsy due to secondary infection and necrosis. The pathology was reported as consistent with large cell NHL and available immunohistochemistry showed lack of expression of CD20, CD3, and cytoketatin. Patient was staged as Ann Arbor stage IEA with no poor prognostic factors according to the International Prognostic Index. The patient was started on CHOP chemotherapy but after two cycles, he had a poor response with a significant increase of the initial lesion and extension to the right upper lip. A repeat biopsy showed a diagnosis of extranodal NK/T-cell lymphoma, nasal type with EBV+.

The patient was switched to combined treatment with methotrexate 3g/m2 on day 1, L-asparaginase 6000U/m2 on day 2, 4, 6 and 8 with dexamethasone 40mg day 1 to day 4 on 21 days cycle for a total of three cycles. The patient responded nicely and the tumor regressed after the first cycle. The patient achieved a complete clinical response after a second cycle (Figure 3). One month after the third cycle, he started irradiation, 30 Gy to the initial site of the disease. At the time of last follow up at 24 months, he was in complete remission (Figure 4). In conclusion, extranodal NK/T-cell lymphoma nasal type is a rare entity. Diagnosis may be difficult without an appropriate panel of immunohistochemistry that may not be available in all hospitals, especially the detection of cytoplasmic expression (CD3ε), EBV expression and molecular biology techniques. Cases with clinical suspicion of extranodal NK/T-cell lymphoma should have a full panel of immunohistochemistry from a tertiary referral center if needed. Conventional anthracycline based therapy (CHOP) has a poor outcome. This could be related to the overexpression of PGP (multi-drug resistance) by NK/T tumor cells. Chemosensitivity to L-asparaginase and high-dose methotrexate has encouraging results and should be tested in future prospective studies. Our patient had 17 years of occupational exposure to iron dusts and galvanized metals (welding) that may have contributed to the development of this type of NHL in our patient.