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Peripheral neuropathy associated with imatinib therapy for chronic myeloid leukemia

TO THE EDITOR: Peripheral neuropathy is a common condition, frequently developing in association with metabolic conditions. It is reported to occur in over 8% of the general population [1] and increases markedly in prevalence over the age of 40 [2]. Pre-diabetes and Type 2 diabetes are currently the most common causes in the world though other disease states may also result in neuropathy.

Many medications, including chemotherapy agents such as vinca alkaloids, platinum-based agents and proteasome inhibitors such as bortezomib, are capable of causing axonal damage and inducing clinical symptoms. Tyrosine kinase inhibitors (TKIs) directed against the BCR-ABL fusion protein, now the mainstay of treatment in chronic myeloid leukemia (CML), have rarely been reported to cause neuropathy. We report here a case of late-onset peripheral neuropathy related to imatinib therapy.

A 41 year old woman attended Princess Margaret Cancer Centre in 2001 after incidental detection of marked leucocytosis on routine blood test. Blood film and bone marrow examination was consistent with chronic phase CML. The diagnosis was confirmed by detection of the BCR-ABL fusion transcript by polymerase chain reaction. She commenced therapy with interferon-α; hydroxyurea was used transiently for cytoreduction. She achieved a complete cytogenetic response and eventually reached an approximately 2-log reduction in BCR-ABL transcript levels.

After five years of continuous therapy with interferon-α she was noted to have a malar rash, elevated anti-nuclear antibody (ANA) and strongly positive rheumatoid factor. After rheumatological opinion, these findings were attributed to a non-specific immunological effect of interferon therapy. Therapy was discontinued and, following an approximately two month period to allow resolution of autoimmune phenomena, she commenced imatinib 400 mg daily. She experienced fluid retention and muscle cramps following introduction of imatinib. Overall, however, she tolerated therapy well and achieved a major molecular response.

In 2016, ten years after commencing imatinib, she described progressive burning sensation associated with numbness in both feet, the anterior part of the lower calves and the left arm. Clinical history did not identify a cause for symptoms. Examination revealed an obese (BMI 46) woman with neurological findings consistent with an axonal neuropathy. Nerve conduction studies were consistent with a mild to moderate axonal neuropathy. Electromyography studies were normal.

Random blood sugar levels and glycated haemoglobin (HbA1c) were normal. Serum levels of vitamin B12 were mildly low in April 2016. Hematological manifestations of B12 deficiency were not observed; neither homocysteine or methyl-malonic acid levels were assayed. B12 levels normalised rapidly with oral B12 supplementation with no change in neuropathic symptoms. Her ANA was positive but rheumatoid factor, ANCA and anti-mitochondrial antibodies were not detected. Other laboratory investigations, including heavy metal assays, were unremarkable.

In addition to neuropathic symptoms, our patient also developed palpitations in 2016. ECG demonstrated a right bundle branch block with left anterior fascicular block. Cardiac MRI, performed given the diagnosis of CML, demonstrated normal biventricular volumes and function; no infiltrative processes were observed. A clear cause for palpitations was not identified at the time of initial work-up but, in mid-2016, she attended the emergency department with symptomatic bradycardia. ECG at this time demonstrated prolonged first degree heart block with intermittent complete heart block. A dual-chamber pacemaker was inserted with resolution of palpitations and bradycardic symptoms. A definitive cause for conducting system disturbance has not been identified.

Neuropathic symptoms were eventually ascribed to imatinib therapy and treatment was temporarily discontinued in January 2017. After a period of 6 weeks some improvement in sensation was observed. Imatinib was re-introduced in March 2017 and, after further deterioration in neuropathic symptoms, was permanently discontinued. Nilotinib 300 mg twice daily was initiated and was well tolerated. Her BCR-ABL transcript has progressively fallen, now showing a 5.3 log reduction (0.0005% by International Scale).

Imatinib has a well-recognised side effect profile, most commonly consisting of fluid retention, including periorbital oedema, gastrointestinal upset including nausea, vomiting and diarrhoea, muscle cramps, skin rash and fatigue [3]. Most side effects occur early in treatment and frequently diminish in severity with time. Late onset toxicity is relatively uncommon and, in particular, unequivocal neurotoxicity is rarely observed.

A review of the literature demonstrates that a single case report of peripheral neuropathy associated with imatinib therapy for CML has been reported [4]. A separate report on ocular adverse events associated with imatinib therapy describes a single case of ptosis which was classified as 'possibly' related to imatinib therapy [5]. Dasatinib has been reported to be associated with optic neuropathy [6] and, more recently, a case of demyelinating peripheral neuropathy [7].

Multiple mechanisms for the onset of peripheral neuropathy following drug therapy have been suggested. It is thought that some combination of mitochondrial dysfunction, inflammatory processes, aberrant cell signalling and disturbance of the ion channels and axonal transport may result in axonal damage and typical symptoms [8].

The mechanism by which imatinib may have caused peripheral neuropathy in this case remains unclear. Imatinib has been reported as causing dose-dependent endoplasmic reticulum stress in cardiac myocytes. This was followed by loss of mitochondrial membrane potential and ultimately cell death [9]. This is of interest given the implication of mitochondrial dysfunction in the onset of chemotherapy-induced peripheral neuropathy and the cardiac manifestations in our patient's case.

A separate report demonstrates that Abl kinases play an essential role in the development of the neuromuscular junction [10]. Abl kinases have also been demonstrated, in *Drosophila* models, to play an essential role in axonal growth [11]. The apparent rarity of neuropathy associated with TKI administration, despite the fact that these agents have been in clinical use for well over a decade, argues against ABL1 inhibition contributing significantly to neuropathy in humans.

In this case, alternative causes for peripheral neuropathy were considered but excluded or felt unlikely. Similar to the previously described case, our patient was treated with interferon-α prior to receiving imatinib therapy. The possibility of peripheral neuropathy relating to interferon therapy, either as a direct effect or due to immunological dysregulation, was considered. However, the onset of symptoms approximately 10 years after interferon discontinuation made this unlikely. Secondly, the reduction in symptoms after imatinib interruption, and their subsequent deterioration following re-introduction, argues in support of imatinib being the causative agent.

Although nilotinib therapy is associated with a higher risk of vascular events [12], this agent was selected given the patient's history of drug-induced autoimmunity. The incidence of dasatinib-associated pleural effusions appears higher in those with prior autoimmune disease [13] and cases of large granular cell lymphocytosis, emerging in the context of dasatinib therapy, are described [14]. The patient's vascular risk factors will be closely monitored and treated to strict targets.

Imatinib is a highly effective therapy for CML though is recognised to have a number of adverse effects. However, neuropathy is rarely associated with imatinib therapy. We outline the second reported case of progressive axonal neuropathy developing in association with imatinib therapy and improving following discontinuation of therapy. Both cases share similarities including prior therapy with interferon-α. Imatinib therapy should be considered as a potential cause for neuropathy in patients developing symptoms while on therapy.

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Primary CNS lymphoma: latest updates and a 10-year monocenter experience

TO THE EDITOR: We read with great interest the paper by Qian and colleagues, which described advances in the treatment of newly diagnosed primary central nervous system lymphomas (PCNSLs) [1]. The authors showed the increasing PCNSL incidence rate and the possible correlation of this increase with the increasing number of immunosuppressed patients. This appealing issue was confirmed in a recently published paper that reported a current Swedish scenario in which the increasing trend was mostly observed among elderly individuals [2].

Qian and colleagues extensively analyzed the available treatment options, such as high-dose methotrexate (HD-MTX) alone or as a component of various MTX-based chemotherapy regimens, whole-brain radiotherapy (WBRT), and surgery. We agree with the authors that HD-MTX should be included in the first-line therapy; according to our knowledge, however, the best available evidence suggests that HD-MTX should be administered in association with high-dose cytarabine to improve both progression-free survival (PFS) and overall survival (OS), as previously suggested [3].

An important goal of PCNSL treatment is survival prolongation with minimal toxicity, especially neurotoxicity. The first randomization of the phase II IELSG32 (the International Extranodal Lymphoma Study Group-32) trial was designed to determine whether rituximab and thiotepa could improve the efficacy of first-line treatment comprising HD-MTX plus HD-cytarabine (MATRix regimen). The complete response (CR) rate among patients receiving HD-MTX plus HD-cytarabine (control arm, arm A) was 23%, compared to 30% in the arm receiving rituximab (arm B) and 49% in the arm receiving both rituximab and thiotepa (group C); here, a multivariate analysis confirmed an independent association between the induction arm and CR rate [4]. The recently published second randomization was designed to investigate the efficacy of WBRT or autologous stem-cell transplantation (ASCT) as a consolidation therapy after induction for patients with chemosensitive PCNSL. Out of 122 eligible patients, 118 were randomly assigned to receive WBRT (group D) or ASCT (group E); both strategies were effective and yielded significantly improved CR rates after induction, with 2-year PFS rates of 80% and 69%, respectively [5]. As expected, hematological toxicity was more common in ASCT arm, while neuropsychological tests demonstrated cognitive impairments in attention and executive functions among patients receiving WBRT [5].

ASCT was previously shown to be high effective as a consolidation therapy with manageable toxicity in phase II trials of patients with chemosensitive PCNSL patients; consequently, an international phase III study is ongoing and