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Case Report

Severe Dizziness and Hypereosinophilia: Coincidence or Complication? A Case Report

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Keywords
Dizziness · Hypereosinophilia · Myeloproliferative neoplasm · PDGFRA rearrangement

Abstract
Hypereosinophilia is a common issue in medicine. One rare cause is myeloproliferative neoplasm with PDGFRA rearrangement. In these patients, the gold standard for therapy is low-dose imatinib. We present the case of a patient with a new diagnosis of myeloproliferative neoplasm following an unconventional diagnostic pattern, which developed clinically relevant unexplained dizziness a week after starting treatment. Our case presented with lower back pain and multiple bone lesions at MRI investigation. Bone marrow and cytogenetic analysis led to the diagnosis of myeloproliferative neoplasm with PDGFRA rearrangement. We started a treatment with a tyrosine kinase inhibitor (imatinib), and the patient noticed an onset of severe, persistent and intense dizziness, which was more intense with closed eyes. Diagnostic tests were not conclusive, and dizziness persisted at 48 months of follow-up. In conclusion, clinically relevant dizziness was never described in patients with myeloproliferative neoplasm. Even if the exact physiopathological mechanism is not clear, clinicians should know that hypereosinophilia could lead to central nervous system damage.

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Background

One rare aetiology of hypereosinophilia is related to a clonal production of eosinophils due to the gene fusion FIP1L1-PDGFRA, as result of deletion at 4q12. This entity is classified as myeloproliferative neoplasm with PDGFRA rearrangement and the common presentation is similar to chronic eosinophilic leukaemia [1]. One important aspect to consider when approaching and treating this syndrome is that eosinophils can secrete many cytokines and other inflammatory factors that could stimulate an important inflammatory response with tissue remodelling provoking potentially irreversible organ damage. The organs most often involved are lungs, heart, gastrointestinal tract, skin and central nervous system [2]. These patients respond very well to low doses of imatinib, a tyrosine kinase inhibitor originally produced for chronic myeloid leukaemia. Low doses of imatinib (100 mg/day) in monotherapy may be adequate to obtain a clinical and molecular response in the majority of patients, while even lower doses can be used as maintenance therapy when a total response is achieved (100 mg/week) [3].

Case Presentation

We report a case of a 60-year-old male patient, in good health status, who has been suffering from lower back pain for several years. An MRI investigation showed multiple bone lesions in the vertebral column and, therefore, the patient was referred to an oncologist for further investigation.

The blood tests found a high leucocytosis of 22,000 U/L with a prevalence of eosinophilic cells (53%) 11,500 U/L, normal haemoglobin and thrombocytes, and high levels of vitamin B_{12} (4,059 pmol/L, range 138–652). We performed a PET scan, which showed an uptake at different vertebral levels (cervical to sacral) being unusual for a metastatic bone disease (Fig. 1A). We then performed a bone scintigraphy, which resulted negative for bone involvement (Fig. 1B); hence, we focussed on a disease which was mainly localized in the bone marrow.

We performed a bone marrow biopsy that showed an increased myelopoiesis with some immature forms and a massive infiltration of eosinophils, most of them already mature (Fig. 2). Immunohistochemical analysis was negative. Because of the strong suspicion of chronic eosinophilic leukaemia, we performed a FISH and cytogenetic analysis and found a FIP1L1-PDGFRA fusion gene diagnostic for myeloid neoplasms with eosinophilia and rearrangement of PDGFRA.

At our first examination, the patient was asymptomatic, except for the aforementioned back pain, and the clinical status was normal. No splenomegaly nor hepatomegaly was present. CT and PET imaging excluded pathological lymphadenopathies.

According to the literature [4], we started a therapy regimen which included imatinib 100 mg/day together with a short-term corticosteroid treatment, not being able to exclude cardiac involvement in a patient with a diagnosis of ischaemic and hypertensive cardiopathy. The patient did not experience immediately adverse events.

Seven days after starting the treatment, the patient noticed an onset of severe and intense dizziness, which was more intense with closed eyes. In fact, with closed eyes, the patient lost his balance and was not able to maintain an upright position. The Romberg test was positive with a high risk of fall with closed eyes. The dizziness was described as subjective and rotatory. The symptom was so intense and persistent to limit the patient's quality of life, forcing him to stop his work in the transport field.

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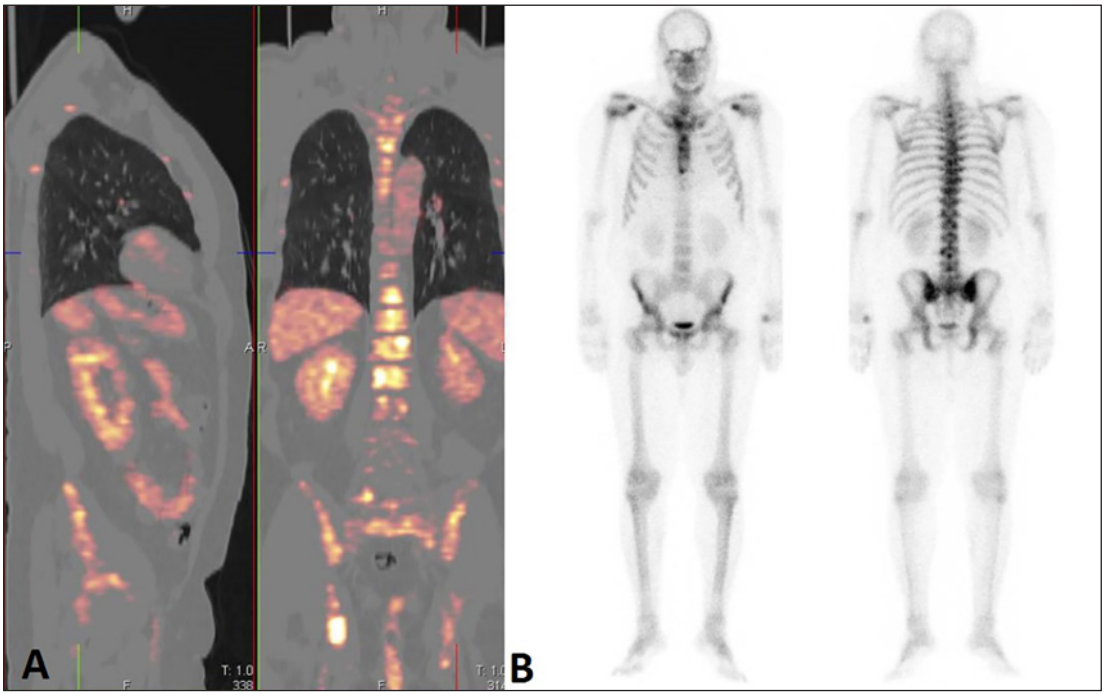

Fig. 1. A PET scan showing an uptake at different vertebral levels. **B** Negative bone scintigraphy.

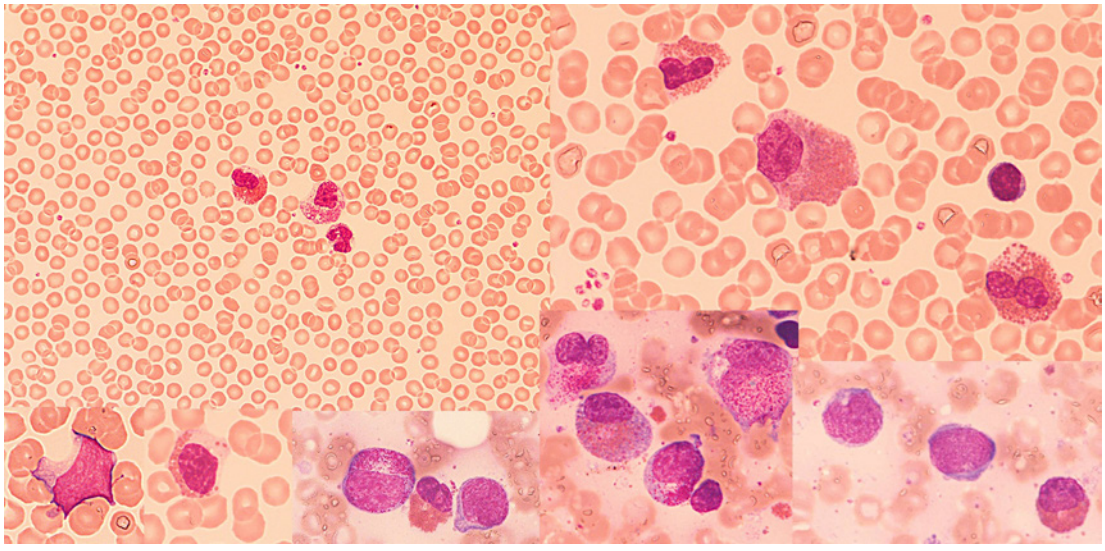

Fig. 2. Bone marrow biopsy showing an increased myelopoiesis with some immature forms and a massive infiltration of eosinophils.

The patient visited an otolaryngologist and all the tests performed were negative (Rinne test, Weber test, no nystagmus, normal motor coordination). A visit at the Department of Neurology including a cerebral MRI clearly excluded central causes of dizziness; even a neurosurgery exam was normal with no clinical signs of myelopathy and a cervical CT scan showed a degenerative picture consistent with the patient's age. Orthostatic hypotension was excluded

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with a negative Schellong test and a clinically negative exam (no variceal veins). Remotely, one might also consider adrenal insufficiency, but our patient did not have new related symptoms such as impotence, nightly diarrhoea, pupil anomalies or sweating disorder.

We speculated that the dizziness might be related to imatinib intake, even though it has never been reported before. The other possible pathogenesis that should be taken into consideration is a central nervous system damage due to hypereosinophilia.

From an oncological point of view, the patient experienced a good response to the current treatment with a clinical response after 2 weeks and complete molecular response after 13 months. Due to the lack of scientific evidence on the length of treatment and the rate of relapse, in agreement with the patient, we did not stop the treatment, despite the persistent dizziness. However, after a few months, dizziness became spontaneously less intense, but the symptoms remained, even if with a lower grade.

After 19 months, considering the great outcome and in order to test the true relationship between dizziness and the drug, we decided to decrease the treatment dose: from 100 mg/day to 300 mg/week and after 27 months, we reduced it to 100 mg/week. At present, the patient is at 48 months of follow-up and has neither a clinical nor molecular relapse of the diseases. Dizziness was reported unchanged even at a lower dose of imatinib.

Discussion and Conclusions

We therefore cannot conclude that there is a real correlation between the drug intake and the reported persistent and severe dizziness, but the suspicion remains moderate and may be explained with a not dose-related mechanism.

We took in the differential diagnosis of orthostatic hypotension, which might lead to the consideration of autonomic neuropathy by either the disease or the drug, and an adrenal insufficiency, but both were excluded due to the absence of related symptoms and the absence of pathological results in clinical and instrumental tests.

Moreover, the other differential diagnosis could be a punctiform permanent damage of the central nervous system. However, we suppose that the damage could be too small to be detected at the radiological exams performed.

To our knowledge, no case of hypereosinophilia with such symptoms has been described so far. Díaz et al. [5] described a case of cerebellar reversible damage with unstable gait and ataxia after 14 days from the diagnosis of idiopathic hypereosinophilic syndrome. They detected hyperintense, vascular-type lesions on T2-weighted images after performing MRI, which resolved after specific treatment. It is also well known that eosinophils may secrete in particular two neurotoxic proteins called eosinophilic cationic protein and eosinophil-derived neurotoxin. Both proteins can cause central nervous system damage as demonstrated in vitro by Navarro et al. [6] with a dose-related mechanism both in astrocytes and in cerebellar granule cells. They saw that metabolic activity of these cells was reduced when the proteins' concentration raised while the apoptosis has increased.

Although our case was different from the one described by Díaz et al. [5] and the MRI lesions were not detectable, the physiopathological mechanism could be similar with a mild involvement of tissue damage at the posterior fossa level due to eosinophil migration to the central nervous system. This could lead to a direct damage related to cytokines and degranulation products secretion, which usually intensify in the first days of therapy with imatinib.

We find our case interesting because of its particular presentation and unconventional diagnostic pattern, as well as the development of clinically relevant dizziness, never described before in association with this pathological entity. Even if the exact physiopathological mech-

anism is not clear in our case, clinicians should know that hypereosinophilia could lead to central nervous system damage and thus patients could develop related symptoms such as dizziness.

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Statement of Ethics

The patient has provided consent to publish these features and the figures of his case and signed a consent form.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

G.L.P. analysed and interpreted the patient data and had the main role in writing the article, B.B. did a critical revision of the article, M.U. did a critical revision of the article, M.R. did a critical revision of the article, O.M. analysed and interpreted the patient data and performed a critical revision of the article. All authors read and approved the final manuscript.

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