

Case Report

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Severe obesity in a patient on long-term treatment of chronic myeloid leukemia with imatinib: Body composition, associated disorders and outcome

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Abstract

Chronic Myeloid Leukemia (CML) is a highly curable malignancy with tyrosine kinase inhibitors (TKI) as target therapy. As treatment is usually prolonged, there is a need to improve our knowledge about the impact of comorbidities in this context. Severe obesity is among the common comorbidities in these patients. We present the case of a patient with morbid obesity and associated sleep apnea hypopnea syndrome who was successfully treated during 14 years with imatinib, a cornerstone TKI for this disease. Visceral fat area was extremely elevated in this patient.

Keywords: chronic myeloid leukemia; obesity; imatinib; sleep apnea hypopnea syndrome.

Abbreviations: CML: Chronic Myeloid Leukemia; BMI: Body Mass Index; TKI: Tyrosine Kinase Inhibitors.

Introduction

Modern treatment of chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKI) is regarded among the most successful developments in cancer medicine [1]. Overweight and obesity are common in many world areas, but there is a very limited knowledge on the impact of obesity in patients treated with TKI for CML [2]. We present the case of a patient who developed severe (morbid) obesity during the treatment with imatinib, with data on body composition, associated disorders and clinical outcome.

Case presentation

A Caucasian woman, born in February 1958, was diagnosed with chronic-phase CML in June 2007. She smoked tobacco until 1985 and had a previous diagnosis of breast cancer in 1993. Sokal and Hasford indexes were 0.72 and 4.13, respectively. Imatinib was started in June 2007 and maintained until June 2021,

with a good clinical and molecular response (RM5). Complete cytogenetic response was obtained at 6 months and major molecular response at 17 months. Maintenance dose of imatinib was 400 mg/day. She was overweight during the adolescence but started to have a marked increase of weight after the diagnosis of CML. Weight in June 2021 was 121 kg, with a BMI of 48. Brachial perimeter: 40 cms. Abdominal perimeter: 129 cms. Hip perimeter: 125 cms. Body composition was studied with the InBody 770 analyzer, showing a normal percentage of fat body mass. The visceral fat area was extremely elevated to 246 cm² (normal <100 cm²) (Figure 1). Study was completed with plethysmography and nocturnal pulsioximetry (Figure 2), suggesting a sleep apnea hypopnea syndrome. Some other events during the period of imatinib treatment with a potential association to obesity included leg deep vein thrombosis that was treated with acenocoumarol, peripheral edema and episodes of leg cellulitis. She needed conventional hospitalization for COVID-19 in November 2020, without complications and with ongoing

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antibody response until March 2021. Relevant drug therapies included long-term omeprazole for reflux esophagitis and to-rasemide for peripheral edema. She remains in complete clinical, cytogenetic and molecular response and in good condition after discontinuation of imatinib, with follow-up in the departments of Hematology, Medical Oncology and Nutrition.

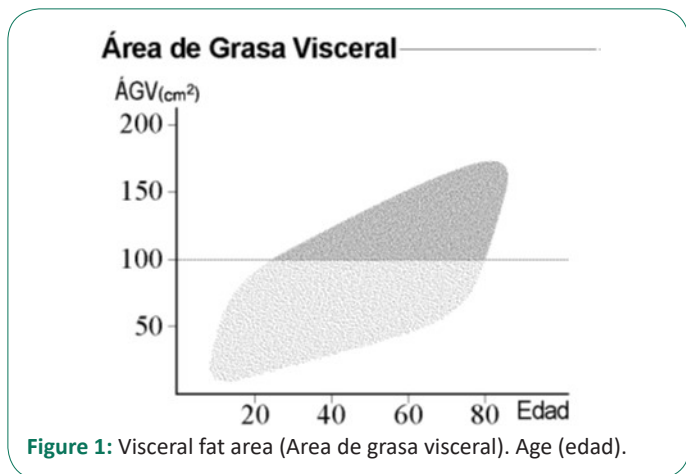


Figure 1: Visceral fat area (Area de grasa visceral). Age (edad).

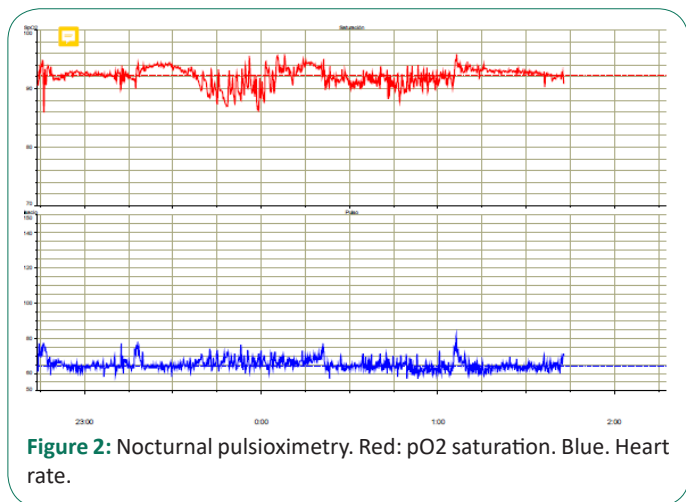


Figure 2: Nocturnal pulsioximetry. Red: pO₂ saturation. Blue: Heart rate.

Discussion

Several meta-analyses have shown an increase of incidence and mortality of CML in obese persons [3-6].

Significant weight gain has been claimed in one review of patients with CML after imatinib therapy, with more of 40% categorized as obese after 24 months of treatment [7], and similar data are available in other studies with wide samples of this group of patients [8,9]. This effect was also present in a series of 1142 surveyed Chinese CML patients treated with TKI. 42% of them referred weight gain, although the incidence was lower in patients treated with imatinib alone [10]. Some authors consider women as more prone to weight gain [11].

In relation to the hematologic outcomes, there have been a few reports in the literature on CML patients with severe obesity and/or bariatric surgery treated with TKI. Interestingly, one case report described a woman with a BMI of 50 and a weight of 122 kg with obstructive sleep apnea syndrome and gastroesopha-

geal reflux who needed a higher dose of imatinib (800 mg/d) to obtain a complete cytogenetic response and was treated later with bariatric surgery [12]. Another report of maintained major molecular response with a dose of 800 mg/d has been described, but the patient was an extreme case of a woman with a BMI of 113 and a weight of 275 kg, different from other case in the same report of a man with a BMI of 51 and a weight of 166 kg who obtained the molecular target with an imatinib dose of 400 mg/d [13]. One further woman with a previous bariatric surgery for weight loss achieved a complete response with 400 mg/d of imatinib, but the authors did not explain if severe obesity was still present [14]. Another case of complete molecular response during the treatment with 400 mg/d of imatinib has been described in a CML woman with morbid obesity [15]. The authors found that bariatric surgery influenced the pharmacokinetics of imatinib, but the patient maintained the complete response with the dose of 400 mg/d. In fact, some authors recommend imatinib over second generation TKI like dasatinib or nilotinib in patients with gastric surgery for morbid obesity [16]. A delay in cytogenetic and molecular responses is another point to consider because it has been reported for patients with high BMI [17]. Nevertheless, that study was directed to patients with BMI >25 and not to patients with severe obesity as a group. The time to the achievement of major molecular response in our case report is closer to their group of patients with low BMI. A Japanese series has reported that patients with lower weight were less likely to obtain a complete cytogenetic response with imatinib [18].

Besides the case report cited previously, sleep apnea hypopnea syndrome has been occasionally reported in patients with CML [19]. Regarding sleep apnea hypopnea syndrome in this context, we must regard that disturbed sleep is described among the most severe symptoms affecting quality of life in CML, and is included in specific questionnaires to evaluate the quality of life in CML patients, as the EORTC QLQ-CML24 [20] and the MD Anderson Symptom Inventory (MDASI) for patients with CML known as MDSA1 [21]. Furthermore, one study has found that a high BMI and disturbed sleep are the most significant factors in relation to fatigue in these patients [22]. Discontinuation of TKI in patients in complete response may improve their quality of life because of a better sleep pattern. More than 20% of patients with CML in complete response participating in The Life After Stopping Tyrosine Kinase Inhibitors (LAST) had a meaningful improvement in sleep disturbances after stopping this treatment [23].

Prevention of cardiovascular toxicity is another important point to consider in CML patients with severe obesity. In fact, diet and weight management have been described as the letter D in the ABCDE steps to prevent cardiovascular disease in patients with CML treated with a TKI [24].

Conclusion

Long-term therapy with a conventional dose of imatinib was successful for inducing and maintaining an adequate response in this patient. No increased doses were needed. Severe obesity developed during the treatment, with a very high area of visceral fat, and was associated to sleep apnea hypopnea syndrome, with a potentially impairing effect on her quality of life.

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