

## CASE REPORT

## Xanthelasma palpebrarum: a new side effect of nilotinib

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**SUMMARY**

Chronic myeloid leukaemia (CML) is a chronic myeloproliferative disorder characterised by a reciprocal translocation between the chromosomes 9 and 22 resulting in constitutionally active tyrosine kinase signalling. BCR-ABL tyrosine kinase inhibitors (TKIs) are highly effective molecules in the treatment of CML. Unfortunately, these novel therapeutic agents are accompanied by various side effects, and haematological, cutaneous and metabolic abnormalities are among the most prevalent. Nilotinib, a second-generation TKI, has been shown to cause both—cutaneous lesions and lipid profile abnormalities. We present two CML cases developing xanthelasma palpebrarum while receiving nilotinib. Case 1 also acquired a lipid abnormality following the start of nilotinib therapy, while case 2 meanwhile stayed normolipidemic. In addition to a low cholesterol diet, atorvastatin was prescribed to case 1. Currently, both cases are normolipidemic and continuing their nilotinib therapy. Xanthelasma palpebrarum secondary to nilotinib therapy is new to the literature.

**BACKGROUND**

Chronic myeloid leukaemia (CML) is a chronic myeloproliferative disorder characterised by a reciprocal translocation between the chromosomes 9 and 22 resulting in constitutionally active tyrosine kinase signalling. BCR-ABL tyrosine kinase inhibitors (TKIs) are highly effective in the treatment of CML, and imatinib mesylate was the first molecule in this novel family of drugs.<sup>1</sup> The appearance of intolerance and resistance to imatinib led to the formulation of second-generation TKIs, for example, dasatinib and nilotinib.<sup>2</sup> While cutaneous adverse effects are the most common non-haematological adverse reactions to TKIs, nilotinib has also been demonstrated to cause metabolic disturbances such as dyslipidaemia.<sup>3 4</sup> We present two patients with CML with xanthelasma palpebrarum secondary to nilotinib therapy as the unusual cause.

**CASE PRESENTATION**

*Case 1:* A 40-year-old woman was referred for investigation of a significant leucocytosis finding. Results of her physical examination were unremarkable. A summary of the relevant laboratory findings are presented in [table 1](#). The patient was diagnosed with BCR-ABL positive, chronic phase CML and started on imatinib 400 mg daily. At the end of the fourth month, as her absolute neutrophil count (ANC) was <1000/μL, the imatinib therapy was interrupted for 3 weeks, with no resolution of

her ANC, a level >1500/μL. Consequently, because of its haematological toxicity, imatinib was not reinstated but, instead, replaced by nilotinib therapy at a dose of 400 mg twice daily. At the end of the 12th month, the patient's BCR-ABL fusion gene levels as determined by qRT-PCR testing were negative.

Fifteen months after starting nilotinib, the patient presented with yellowish plaques around her eyelids. Physical examination revealed lesions consistent with xanthelasma palpebrarum ([figure 1](#)). Repeated medical history-taking documented no systemic disorders as potential causes. The patient denied smoking and consuming alcohol, and was not using any medications other than nilotinib. Her family history was also unrevealing. The patient's repeated lipid profile is given in [table 1](#).

*Case 2:* A 29-year-old woman presented for investigation of a leucocytosis finding. The results of a physical were unremarkable. Her initial laboratory results are summarised in [table 1](#). Subsequently, the patient was diagnosed as being BCR-ABL positive and having chronic phase CML. Imatinib therapy at a dose of 400 mg daily was started. During the fourth month of therapy, grade 3–4 haematological toxicity pertaining to thrombocytes developed. On the occurrence of thrombocytopenia with a count <50 000/μL, imatinib therapy was interrupted for a period of 2 weeks. Unfortunately, the thrombocyte count did not increase to a level >50 000 μ/L and therefore imatinib was stopped and therapy switched to nilotinib (400 mg twice daily).

During the sixth month following the start of nilotinib therapy, the patient developed yellow coloured elevated lesions around both her eyelids. Repeated physical examination revealed findings consistent with xanthelasma palpebrarum ([figure 2](#)). Detailed medical history-taking did not document any systemic disorders, and the patient denied drinking alcohol and smoking tobacco, and was not using any medications other than nilotinib. Family history of the patient was also unremarkable. A repeated lipid profile of the patient is displayed in [table 1](#).

**INVESTIGATIONS**

While the baseline lipid profile of case 1 was normal, her lipid profile at the 15th month of nilotinib therapy displayed marked elevations of low-density lipoprotein (LDL-C) and total cholesterol (TC) together with triglycerides (TG). Case 2 demonstrated a normal lipid profile both initially and while she presented with lesions of



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**Table 1** Relevant laboratory findings of case 1 and case 2 before and after nilotinib therapy

Laboratory parameters	Case 1		Case 2	
	Before nilotinib	15th month of nilotinib therapy	Before nilotinib	6th month of nilotinib therapy
Haemoglobin (11.7–17.0 g/dL)	11.8	–	13.3	–
Leucocyte (4.6–10.2×10 <sup>3</sup> /μL)	<b>62.30</b>	–	<b>26.30</b>	–
Neutrophil (2.0–7.0×10 <sup>3</sup> /μL)	<b>58.2</b>	–	<b>21.2</b>	–
Platelet (142.0–424.0×10 <sup>3</sup> /μL)	349	–	233	–
<i>BCR/ABL</i> (breakpoint cluster region-Abelson)	<b>90.1%</b>	–	<b>92.0%</b>	–
<i>Jak2</i> mutation	Negative	–	Negative	–
Total cholesterol (130–200 mg/dL)	150	<b>300</b>	150	<b>147</b>
LDL cholesterol (60–130 mg/dL)	90	<b>220</b>	82	<b>80</b>
Triglycerides (50–150 mg/dL)	100	<b>180</b>	94	<b>90</b>

Laboratory results falling out of the reference ranges are designated in bold  
LDL, low-density lipoprotein.

xanthelasma palpebrarum (at the sixth month of nilotinib therapy) (table 1). Both cases had normal fasting plasma glucose levels, normal hepatic, renal and thyroid function tests and normal pancreatic lipase/amylase levels.

**DIFFERENTIAL DIAGNOSIS**

The typical differential diagnosis of xanthelasma palpebrarum includes familial hyperlipidaemias (ie, types II, III and IV), dyslipidaemias characterised by low high-density lipoprotein (HDL) cholesterol levels, uncontrolled diabetes and atypical lymphoid infiltrates. The unrevealing family histories, normal fasting plasma glucose levels and the myeloid origin of the underlying haematological neoplasm make these differential diagnoses highly unlikely.

**TREATMENT**

Case 1 was counselled to strictly adopt a low-cholesterol diet, perform regular aerobic exercise and start a course of 20 mg of atorvastatin daily. Nilotinib therapy (400 mg twice daily) was not interrupted. As case 2 was normolipidemic, neither a diet change nor a course of statin treatment was implemented. She also continued her nilotinib 400 mg twice daily therapy.

**OUTCOME AND FOLLOW-UP**

Both cases are currently normolipidemic and on nilotinib therapy. Case 1 did not experience any statin related side effects. Her creatinine kinase and alanine aminotransferase (ALT) levels were monitored and found to be within normal limits.

**DISCUSSION**

In recent years, several TKIs have been developed and received approval for CML treatment. The safety of these drugs is becoming an important issue. Although not life-threatening, skin problems constitute the most common untoward effects of these novel therapeutic agents.<sup>3</sup>

Skin rash associated with imatinib therapy is generally mild and is often characterised by maculopapular lesions. It has been shown that imatinib causes grade 1–2 skin rashes in 30–40% of patients, pruritus in 7.3% of patients, alopecia in 4.4% of patients, increased sweating in 3.6% of patients, stomatitis in 2.9% of patients and dry mouth in 2.2% of patients using it.<sup>5</sup>

The cutaneous side effects of dasatinib were noted from one phase I and five phase II trials, collectively, from a total of 911 patients with CML. Dasatinib was associated with a 35% risk of cutaneous reactions. Most frequent side-effects consisted of localised/generalised erythaema, maculopapular eruptions and exfoliative rashes. Most of these were grade 1–2 lesions. Pruritus was observed in 11% of patients while mucositis and stomatitis were present in 16% of patients.<sup>6</sup> A rare side effect of panniculitis presenting with painful subcutaneous nodules was reported in two patients with chronic phase CML receiving dasatinib treatment.<sup>7</sup> Also, very few cases of pustular rashes and acne-like eruptions associated with dasatinib therapy are described in the literature.

Likewise, patients and their clinicians frequently encounter cutaneous side-effects of nilotinib therapy. In a phase I study of nilotinib in 119 leukaemic patients, Kantarjian *et al*<sup>8</sup> reported cutaneous side-effects in the form of grade 1–2 lesions. The most frequent untoward cutaneous effects were pruritus



**Figure 1** Xanthelasma palpebrarum of the superior and inferior palpebrae (case 1).



**Figure 2** Xanthelasma palpebrarum of the superior and inferior palpebrae (case 2).

(2–15%), non-specific rashes (2–20%), dry skin (0–12%) and alopecia (0–6%), all of which appeared to be dose related. Another, this time a phase II study conducted on 280 patients, demonstrated the appearance of non-specific rashes in 28% and pruritus in 24% of the treated patients.<sup>9</sup>

Non-cutaneous adverse events resulting from nilotinib therapy included reversible constitutional symptoms, and elevations in ALT, aspartate transaminase, lipase, bilirubin, fasting plasma glucose and plasma lipid concentrations.<sup>10</sup> Hypercholesterolaemia, hyperlipidaemia and hypertriglyceridaemia are mentioned as side effects by the manufacturer. Product instructions do suggest assessing the plasma lipid profile both prior to and during nilotinib therapy as clinically indicated. Rea *et al* showed a significant rise in TC within 3 months of initiation of nilotinib therapy in a pattern involving elevation of both, LDL and HDL cholesterol fractions. Although the mechanism of nilotinib-associated dyslipidaemia is not fully understood, it is thought to be due to increased hepatic synthesis and/or impaired clearance from the blood.<sup>4</sup>

Xanthomas form as foam cells cluster in the connective tissues of the skin, tendons or fasciae. Foam cells are macrophages loaded with excessive amounts of LDL particles and their oxidised forms. From a pathological viewpoint, the following factors may take part during the formation of xanthomas: (1) high local concentrations of lipids in the connective tissue; (2) the presence of qualitatively different lipoproteins at normal plasma lipid concentrations; (3) increased extravasation of lipids due to increased vascular permeability, increased local circulation or chronic inflammation; (4) lipid synthesis in situ and their deposition in histiocytes; (5) dysfunction of the reverse cholesterol transport.<sup>11 12</sup>

Xanthelasma palpebrarum is the most commonly observed form of xanthomas and most commonly identified in subjects over 50 years of age. About half of these subjects have underlying dyslipidaemia (high LDL-C and TG, low HDL-C and apo A-1).<sup>13</sup> The presence of xanthelasma palpebrarum should not be underestimated in clinical practice.

With respect to cases presented, while case 1 was demonstrating a markedly abnormal lipid profile, case 2 had xanthelasma palpebrarum lesions while exhibiting a normal lipid profile. Consequently, while in case 1 xanthelasma palpebrarum was associated with a nilotinib-induced dyslipidaemia, in case 2, it could be associated with a nilotinib-induced presence of qualitatively different lipoproteins at normal plasma concentrations, or increased extravasation of lipids, or lipid synthesis in situ together with deposition in histiocytes.

The findings pertinent to case 2 suggest that xanthelasma palpebrarum may appear as a cutaneous side effect of nilotinib therapy, independent of hyperlipidaemia. To the best of our knowledge, there have been no reported cases of xanthelasma palpebrarum observed in patients treated with nilotinib. In case 2, even though the appearance of xanthelasma palpebrarum without associated hyperlipidaemia may have been an incidental co-occurrence, we strongly believe that this cutaneous untoward effect should be noted in the literature and required attention should be placed on it. However, studies including larger cohorts are surely needed to confirm xanthelasma palpebrarum as a cutaneous side effect of nilotinib.

## Learning points

- ▶ Patients with chronic myeloid leukaemia should be screened for lipid disorders prior to and during nilotinib therapy.
- ▶ Patients with hyperlipidaemia secondary to nilotinib therapy should receive dietary advice and, if needed, lipid-lowering agents should be added to the therapy.
- ▶ Xanthelasma palpebrarum should be considered an untoward effect of nilotinib, independent of the presence of hyperlipidaemia.

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