

## Case Report

# Using intralesional corticosteroids to treat significant periorbital oedema due to imatinib

## 以病灶內注射皮質類固醇治療伊馬替尼引致的嚴重眼眶周圍水腫一例

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We report the first case of intralesional corticosteroids being successfully used to treat significant periorbital oedema secondary to imatinib therapy. The patient's quality of life was significantly impaired as a result of her ongoing imatinib treatment for an underlying malignancy. While this approach mitigates the risks associated with surgery, in rare cases it can result in retinobulbar vascular occlusion from crystalline corticosteroid aggregates. Accordingly, periorbital corticosteroid injections should only be considered as a treatment option in carefully selected patients. Fortunately, our patient has thus far enjoyed a favourable outcome, with minimal periorbital oedema observed two years after dermatological intervention.

我們報告首宗病灶內注射皮質類固醇成功治療伊馬替尼引致的嚴重眼眶周圍水腫個案。個案中，病人因為患有癌症，需要持續使用伊馬替尼治療，生活質素深受藥物副作用影響。雖然注射方法相對手術來說風險較少；但在極少的個案中，它可能會因皮質類固醇的結晶集合體而導致視網膜脈絡膜血管閉塞。因此，在考慮眼眶周圍皮質類固醇注射治療方案時，必須小心篩選合適患者。幸運地，在皮膚科治療計起兩年後，我們的病人迄今仍保持良好療效，只有些微的眼眶周圍水腫。

**Keywords:** Gastrointestinal stromal tumours, imatinib, periorbital oedema, intralesional steroid injections, quality of life improvement

**關鍵詞：**胃腸道基質瘤、伊馬替尼、眼眶周圍水腫、病灶內注射類固醇、生活質素改善

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## Introduction

We report a case of intralesional corticosteroids being used to treat significant periorbital oedema in a 71-year-old woman with gastrointestinal stromal tumour (GIST). The bilateral periorbital oedema, secondary to imatinib mesylate therapy, impaired her visual fields bilaterally and disturbingly impacted on her quality of life. Previously, only two cases of imatinib-associated

periorbital oedema were reported to have been successfully treated with surgical blepharoplasty. These patients had chronic myelogenous leukaemia (CML) rather than GIST.<sup>1,2</sup> Medical management of the oedema with topical hydrocortisone, diuretics, salt and fluid restriction has been unsuccessful to date.<sup>2,3</sup> This is the first case report of intralesional corticosteroids being used to successfully treat imatinib-induced periorbital oedema.

## Case report

Our patient was diagnosed with advanced GIST in November 2008, with peritoneal and hepatic metastases. Her past medical history includes hypertension, hypercholesterolaemia, peripheral vascular disease, childhood rheumatic fever, osteoarthritis and heavy smoking. She was commenced on 100 mg daily of imatinib in November 2008. Four months later she developed lower eyelid oedema obstructing her visual fields bilaterally. Examination by an ophthalmologist did not demonstrate any deficits in corrected visual acuity. However, our patient reported difficulties wearing spectacles due to significant periorbital oedema. Her oedema deteriorated following a dose increase to 200 mg daily in December 2009. She was an avid reader and was no longer able to enjoy reading. Moreover, her facial appearance caused her considerable distress, and her obstructed visual fields made her reticent to go outdoors. This impaired her quality of life, with a consequence consistent with a severity grade of three using the Common Terminology Criteria for Adverse Events (CTCAE).

Our patient sought treatment for her periorbital oedema in September 2010 (Figure 1). A punch biopsy of the increasingly oedematous right lower eyelid was performed to exclude a cutaneous malignant infiltrate. This showed moderate dermal oedema, with separation of collagen fibres, a small number of mast cells and stellate dendritic cells and a focal, mild perivascular lymphocytic

infiltrate. There was no evidence of dysplasia or malignancy. However, the periorbital oedema persisted. A further biopsy was obtained from the right lower eyelid in May 2011. This again showed marked dermal oedema and scattered interstitial mast cells. The benign histology was thought to be consistent with a chronic imatinib-induced reaction.

After a detailed discussion between the patient and the senior author regarding potential benefit and risks of intralesional steroid injections in this clinical setting, the patient decided to try intralesional steroids. Initially triamcinolone acetonide 10 mg/ml was injected into the oedematous areas bilaterally, with a fair distance inferior to the lower eyelid margins. Subsequently, five injections of triamcinolone acetonide 40 mg/ml were carefully administered at about monthly intervals to the right lower eyelid until November 2012. Only one injection of triamcinolone acetonide 40 mg/ml was administered into the left lower eyelid since the patient was already satisfied with the progress made. These injections resulted in a significant reduction in the periorbital oedema and an improvement of her visual field restriction. Furthermore, the patient was most delighted by the re-appearance of her lower eyelid wrinkles! On review in June 2013, improved periorbital oedema was still evident under the eyelids (Figure 2). Nonetheless, our patient was informed of the possibility of gradually worsening oedema as long as imatinib therapy is continued for her GIST.

## Discussion

Imatinib is a protein-tyrosine kinase inhibitor which has been in use for over 10 years in the treatment of unresectable or metastatic GIST. Inhibition of KIT and platelet-derived growth factor receptor (PDGFR) tyrosine kinases disrupts phosphorylation of substrate proteins, which inhibits downstream signalling pathways involved in GIST cell proliferation and increases cancer cells' sensitivity

to apoptosis triggers.<sup>4</sup> Imatinib is generally well-tolerated, and is also used to treat CML.<sup>5</sup> Periorbital oedema is a common adverse effect of imatinib, affecting 48.6%-70.0% of patients.<sup>6-8</sup>

There are a number of differential diagnoses for localised periorbital oedema (Table 1). Allergic and irritant contact dermatitis, with or without secondary infection, can result in localised swelling of facial and periorbital skin. Acute or recurrent erysipelas can simulate this clinical scenario, particularly in older and immunocompromised patients. Pre-septal cellulitis may also cause localised periorbital erythema and swelling, which may be associated with fever. Connective tissue diseases can result in facial oedema, with systemic lupus erythematosus and dermatomyositis as important examples. Facial lymphoedema can also arise from persistent acne rosacea. Blepharochalasis may cause recurrent episodic eyelid oedema, while parasitic infections including trichinosis and American trypanosomiasis may induce persistent periorbital oedema. Chronically undiagnosed or untreated hypothyroidism may lead to swelling of the face and lips associated with infiltration of glycosaminoglycans into the skin. Superior vena cava syndrome caused by



**Figure 1.** The patient's periorbital oedema in September 2010.



**Figure 2.** The patient's appreciably improved periorbital oedema in February 2013.

**Table 1.** Differential diagnoses of periorbital oedema

Cause	Description
Irritant or allergic contact dermatitis	Commonly arising from cosmetics and other topical preparations
Pre-septal cellulitis	Infection of the skin around the eyelid presenting with pain, erythema and oedema. The patient may be febrile.
Autoimmune disorders	Systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis and dermatomyositis may result in facial oedema
Hypothyroidism	Infiltration of glycosaminoglycans into skin may cause swelling of the face and lips
Acne rosacea	May cause facial lymphoedema
Blepharochalasis	May cause recurrent episodic eyelid oedema
Superior vena cava syndrome	Venous engorgement of the face and upper limbs caused by tumours of the head and neck, Pancoast tumours and lymphoma
Parasitic infections	Trichinosis and Trypanosomiasis may cause persistent periorbital oedema

tumours of the head and neck, Pancoast tumours and lymphoma may cause oedema and venous engorgement of the face and upper limbs. Finally, Melkersson-Rosenthal syndrome can cause recurrent swelling of the cheeks and lips.

Periorbital oedema from imatinib is thought to occur because of its interactions with dermal dendrocytes, the predominant cell population in periorbital skin. Dermal dendrocytes express c-KIT and PDGFR tyrosine kinases, the molecular targets for imatinib, and may also have a role in promoting mast cell degranulation.<sup>9</sup> Inhibition of the PDGFR receptor results in decreased tissue hydrostatic pressure in the dermis and an increased transportation of particles from the capillaries to the interstitium, thus promoting a flow of fluid into the interstitium. In addition, local anatomical factors such as the closed spaces formed by collagenous septal attachments and relatively poor lymphatic drainage from the bony orbit, contribute to the development of oedema.<sup>1,9</sup> The apparent effectiveness of intralesional steroids in settling the periorbital swelling could be partly attributed to this.

Amongst the cases of imatinib-related periorbital oedema, it has been reported that 98.6% had oedema of mild to moderate severity (CTCAE grade one or two) and no treatment is required.<sup>6</sup> However, 1-5% of patients experience grade three oedema, which may be associated with pleural or pericardial effusions, pulmonary oedema or ascites.<sup>1,6,10</sup> The degree of periorbital oedema appears to be dose-dependent, with those receiving more than 400 mg/day having higher rates.<sup>7</sup>

Medical management of periorbital oedema to date includes topical hydrocortisone, hydrochlorothiazide diuretics and salt and fluid restriction.<sup>11</sup> In one case report, a 70-year-old man with CML treated with imatinib (400 mg-600 mg/day) developed severe periorbital oedema, which responded only minimally to a regimen of fluid restriction, a low-salt diet and topical

hydrocortisone cream.<sup>3</sup> In another, a 63-year-old man with CML treated with imatinib (400 mg-600 mg/day) developed lower eyelid festoons causing visual obstruction. Similar to our patient, he was unable to wear spectacles due to the severity of his lower eyelid oedema. A surgical debulking of the excessive oedematous skin and fat was successfully performed using a subciliary approach, with no recurrence seen six months post-surgery. However, ectropion of the lateral eyelid was reported.<sup>1</sup>

In a third case, a 70-year-old man with CML treated with imatinib (400-600 mg/day) developed severe periorbital oedema with a disruptive superior visual field defect. This failed to respond to a regimen of fluid restriction, a low-salt diet, head of the bed elevation and topical hydrocortisone cream. Bilateral upper and lower eyelid blepharoplasty was performed with good results, with no recurrence 17 months post-surgery. However, post-operative bleeding requiring transfusion occurred. This was attributed to CML-associated thrombocytopaenia.<sup>2</sup>

While intralesional steroid injections potentially mitigate the risks of bleeding, scarring and ectropion, there is a well-described risk of retinochoroidal vascular occlusion caused by crystalline corticosteroid aggregates acting as micro-emboli. Consequently, blindness is a rare but serious complication following intralesional steroid injection in the periorbital region.<sup>12</sup> A systematic review identified thirty-two patients developing blindness after facial injections, fifteen of whom were injected with adipose tissue and 17 were injected with various other materials including corticosteroids.<sup>13</sup>

As a result, the following recommendations were developed: use smaller-sized needles; use lower injection pressures; inject as little volume as possible; avoid pre-traumatized tissues; and aspirate first to exclude intravascular needle placement.<sup>13</sup> Another study also found that limiting the volume of injected corticosteroid may reduce

the risk of micro-embolisation.<sup>14</sup> With this risk in mind, intralesional steroid injection should not be routinely considered and performed unless the patient suffers a significant quality of life impairment. In this case, the patient endured an obvious quality of life impairment due to her ongoing treatment for an underlying malignancy. Fortunately, at the time of writing, there has been no obvious resurgence of the patient's periorbital oedema.

## Conclusion

As far as the authors are aware, this is the first case report of intralesional corticosteroids being used successfully to treat significant periorbital oedema secondary to imatinib. This non-surgical approach avoids the risks associated with surgery such as infection, bleeding and ectropion. However, it is important to recognise retinochoroidal vascular occlusion as a rare but potentially serious complication. Fortunately, our patient has thus far enjoyed a favourable outcome, with minimal periorbital oedema observed at least two years after dermatological intervention.

## Declaration of interest

The authors are not affiliated with any commercial organisation, and there are no conflicts of interest to declare.

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