Case series – Scrotal edema associated with zanubrutinib

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INTRODUCTION

Zanubrutinib, a second-generation Bruton's tyrosine kinase (BTK) inhibitor, was appoved in the U.S. in 2019 and by Health Canada in 2021 for the treatment of mantle cell lymphoma, and has demonstrated efficacy in other B-cell malignancies, including chronic lymphocytic leukemia (CLL) and Waldenström macroglobulinemia.[1,2] As a second-generation BTK inhibitor, it has been designed to improve selectivity and minimize off-target effects compared to first-generation drugs.[1] Despite its therapeutic benefits, zanubrutinib is associated with well-documented adverse effects, most commonly arrhythmia, hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, as well as gastrointestinal symptoms like diarrhea.[3,4]

We report three patients undergoing treatment for hematologic malignancies who developed isolated scrotal and penile edema while receiving 320 mg daily zanubrutinib therapy — an adverse event not previously documented with this medication. Fluid retention is a well-documented adverse effect of BTK inhibitors, commonly presenting as pleural and pericardial effusions, as well as peripheral and generalized edema.[4] First- and second-generation BTK inhibitors, such as imatinib and dasatinib, have previously been associated with scrotal and penile edema, suggesting a potential class-wide effect;[5,6] however, to our knowledge, the cases described in this report represent the first documented instances of isolated scrotal and penile edema associated with zanubrutinib treatment.

CASE REPORTS

Case 1

A 59-year-old man was diagnosed with CLL in 2005. Comorbidities include type 1 diabetes mellitus, obesity, hypertension (HTN), and hyperlipidemia (HLD). This patient was initially treated for CLL with the first-generation BTK inhibitor ibrutinib (420 mg daily); however, due to worsening hypertension, his therapy was switched to zanubrutinib (320 mg daily).

Three months after initiating zanubrutinib, he developed swelling, erythema, and pruritus of the penis and scrotum, with the scrotal rugae preserved. Computed tomography scan of the abdomen and pelvis (CTAP) imaging revealed scrotal edema extending to the base of the penis.

Initial management included a trial of Bactrim for suspected cellulitis; however, there was no improvement in symptoms at one-month followup. Given the lack of improvement, the patient was advised to discontinue zanubrutinib for one month. During this period, his rash resolved, and his edema improved significantly. Given the overall improvement of symptoms, the patient was advised to cautiously resume zanubrutinib therapy at the original dosage while being monitored for recurrence of edema or other adverse effects. Two months after resuming the therapy, scrotal edema has remained mild.

Case 2

A 62-year-old man was diagnosed with splenic marginal zone lymphoma (MZL) in 2019. Comorbidities include HTN and HLD. He was initially managed with two years of rituximab therapy when a right orbital mass was discovered and biopsied to reveal MZL. A full-body computed tomography (CT) scan showed bony changes and uncertain pancreatic involvement, prompting the initiation of zanubrutinib 320 mg daily. Obinutuzumab was added in combination with this therapy one year later. Five months after the start of this combination therapy (17 months on zanubrutinib), the patient presented to the emergency room (ER) with complaints of painless scrotal swelling, along with discoloration of the scrotum (dark red/purple), which developed over the course of a week.

In the ER, the patient denied trauma, fever, dysuria, or a history of sexually transmitted disease. Upon examination, the patient exhibited bilateral scrotal edema

that notably differed from typical anasarca, with preserved scrotal rugae. Scrotal ultrasound was performed, which confirmed the presence of scrotal edema, normal testicles, and normal Doppler flow. The patient was discharged with a two-week course of fluconazole for suspected fungal involvement contributing to scrotal discoloration. The patient was also advised to abstain from sexual intercourse for four weeks and to halt zanubrutinib therapy for one month. The decision to recommend suspension of Zanubrutinib therapy in this case was based on experience from the prior two patients.

After one month off zanubrutinib therapy, the patient reported complete resolution of scrotal swelling. Given this improvement, the patient was rechallenged with a reduced daily dose from 320 mg to 160 mg zanubrutinib, while closely monitoring for recurrence of symptoms. One month after initiating reduced-dose therapy, there has been no recurrence of scrotal edema.

Case 3

An 81-year-old man was diagnosed with CLL in 2009. Comorbidities include HTN, HLD, and coronary artery disease (CAD). He began taking zanubrutinib 320 mg daily for CLL, and after 28 months of treatment, he presented with complaints of painless scrotal swelling and a pruritic inguinal rash of two months' duration, with scrotal rugae notably preserved. The patient denied systemic symptoms, including fever, dysuria, and shortness of breath.

On examination, bilateral scrotal edema was observed, extending to the base of the penis. A CTAP was performed for further evaluation, confirming the presence of bilateral scrotal edema extending to the base of the penis (Figure 1).

Initial management included treatment with clotrimazole for the inguinal rash and discontinuation of the patient's buproprion treatment for six weeks. Conservative measures, such as scrotal elevation with supportive underwear and avoidance of new soaps, detergents, or topical powders, were also recommended. Despite these interventions, the edema persisted without any improvement.

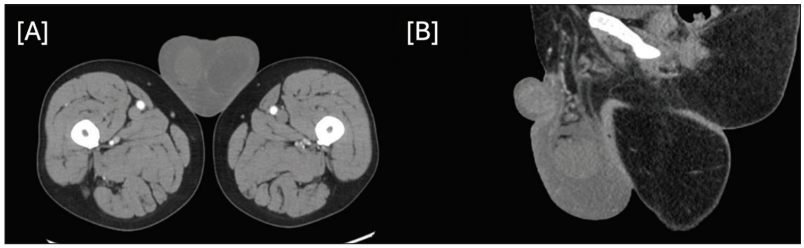

Figure 1. Computed tomography images demonstrating scrotal edema with diffuse soft tissue edema and free water accumulation in the scrotal region. Panel A shows an axial view, while panel B presents a sagittal view

As a next step, the patient was advised to temporarily discontinue zanubrutinib for one month. This break from the medication resulted in a significant improvement in the edema. Given this progress, zanubrutinib therapy was resumed at the original dose (320 mg daily). The edema completely resolved approximately six months later while continuing treatment, with no recurrence of symptoms to date.

DISCUSSION

While the action of BTK inhibitors is intended to be selective to B-cell receptor-signaling mechanisms, unintended effects can occur. The occurrence of scrotal edema in patients receiving zanubrutinib therapy is a novel clinical observation that necessitates examination of potential underlying mechanisms and clinical implications. Awareness of this potential side effect is essential for ensuring effective and safe management, while avoiding unnecessary treatments and interventions.

The cases presented herein describe a temporal relationship between zanubrutinib therapy and the onset of scrotal edema. In each case, cessation of zanubrutinib therapy resulted in either a partial or complete resolution of symptoms, indicating a potential causative link between the medication and the development of scrotal edema. The absence of infectious, malignant, or autoimmune etiology supports the hypothesis that zanubrutinib was the precipitating factor.

Fluid retention in various forms is a commonly reported adverse effect of the BTK inhibitor class, including pleural and pericardial effusions, as well as peripheral and generalized edema, most frequently affecting the periorbital region and lower extremities.[4] An increased risk of edema has been noted in patients over 65 years of age, and all patients receiving this class of medication are advised to undergo continuous monitoring of body weight, peripheral tissue tone for pitting edema, and cardiopulmonary function.[7]

Edema associated with BTK inhibitors is typically reversible, often resolving upon drug discontinuation.[7] One potential mechanism for this adverse effect may involve medication-induced alterations to vascular permeability.[8] Dasatinib, another second-generation BTK inhibitor, has previously been shown to cause pleural effusion in a reactive oxygen species-dependent manner, ultimately leading to increased paracellular permeability and fluid extravasation.[9]

It is feasible that zanubrutinib produces a similar effect on vascular permeability in the scrotum, leading to fluid extravasation and resultant edema. Because scrotal and penile edema have been documented

in association with both first-generation and other second-generation BTK inhibitors, the occurrence of this adverse effect may be a class-wide phenomenon, reducing the number of viable alternatives for patients.[5,6]

Importantly, similar genital cutaneous toxicities have been reported with other tyrosine kinase inhibitors, notably sunitinib and cabozantinib. Sunitinib has been associated with severe genital erythema, scaling, and ulceration, sometimes necessitating treatment interruption or dose reduction. These reactions can occur within the first month of therapy and may recur upon rechallenge, highlighting the need for early recognition and management.[10-14]

Cabozantinib, a multitargeted tyrosine kinase inhibitor, has also been linked to a high incidence of cutaneous adverse effects, including scrotal erythema and ulceration, with up to 15% of patients developing genital skin toxicity. These reactions often require dose modification or discontinuation and can significantly impact quality of life and adherence to therapy.[15] The pathophysiology of these reactions is thought to involve disruption of vascular and lymphatic integrity, as well as direct effects on skin and mucosal tissues.[12,15,16]

Given the efficacy of zanubrutinib therapy in the treatment of B-cell malignancy, discontinuation of the treatment may not always be feasible. This poses a challenge in the clinical management of this adverse effect. Swelling of the scrotum or the penis, even when benign and reversible, can cause significant anxiety and discomfort for patients. While the swelling was not associated with pain in these cases, the psychological impact can be considerable. In addition to psychological distress, scrotal swelling can contribute to physical discomfort and interfere with activities of daily living, such as sitting, exercise, or sexual activity.

Importantly, recognizing that scrotal edema can be an adverse effect of zanubrutinib therapy may help avoid unnecessary hospital admissions and empiric treatment. In case 1, the patient was initially treated with antifungals under the suspicion of infection, a common occurrence in immunocompromised populations. Awareness of zanubrutinib-induced scrotal edema can help clinicians to distinguish between infectious and non-infectious processes earlier, potentially avoiding unnecessary forms of management.

CONCLUSIONS

Our three cases demonstrate that isolated penile and scrotal edema can develop during zanubrutinib therapy. Recognizing this association is crucial to minimizing unnecessary diagnostic tests and interventions in affected patients. Further investigation into the mechanisms underlying this adverse effect will be essential for optimizing management strategies and ensuring patient safety during treatment.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

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