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TYROSINE-KINASE-INHIBITOR-INDUCED PENO-SCROTAL LYMPHEDEMA AND FUNCTIONAL ISSUES OF THE LYMPHATIC PATHWAYS: A CASE REPORT AND COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT

Tyrosine kinase inhibitors (TKIs) are widely used in oncology and hematology. While chylous pleural and pericardial effusion have been described, peripheral lymphedema with administration of acalabrutinib has not been documented. Clinical and imaging data were retrospectively collected from the medical record of an 80-year-old patient with a prior history of radical prostatectomy and pelvic lymphadenectomy who was treated with acalabrutinib for chronic lymphocytic leukemia (CLL). A Medline review (from database creation to October 2025) and pharmacovigilance database searches were conducted to identify TKI-related lymphatic complications. The patient developed progressive peno-scrotal lymphedema after acalabrutinib initiation. Cardiac and venous evaluations were normal. MR-lymphography showed patent central lymphatic pathways and superficial peno-scrotal edema. Dynamic lymphangiography revealed no obstruction or leak, suggesting functional impairment of lymphatic drainage. Literature review identified 28 relevant articles, including 20 cases of chylothorax, mainly under dasatinib, and additional cases of chylous ascites and chylopericardium. To our knowledge, no previous case of TKI-induced lymphedema has been published. Pharmacovigilance databases identified few lymphatic adverse events, including 24 cases of lymphedema in the FAERS database. This first report of TKI-induced lymphedema broadens the spectrum of lymphatic complications associated with these agents and highlights the potential concept of functional rather than obstructive lymphatic impairment.

Keywords: Tyrosine kinase inhibitors; Chylous leak; Central conducting lymphatic anomalies; Drug-related adverse event; Scrotal lymphedema

INTRODUCTION

Protein-tyrosine kinases (PTKs) are criti-

cal components of signaling pathways that control cellular proliferation and differentiation. Tyrosine kinase inhibitors (TKIs) have thus become a cornerstone in the treatment of various hematological malignancies and solid tumors. While their safety profile is generally favorable, TKIs are associated with a range of adverse events, among which serosal effusions and edema are common. In some cases, these effusions have been characterized as chylous, suggesting a potential impact of TKIs on the lymphatic system. Beyond TKIs, other hematologic and oncologic agents such as mTOR inhibitors (e.g., sirolimus) are also known to cause lymphedema through altered lymphangiogenesis and lymphatic endothelial dysfunction. This supports the concept that drug-related lymphatic impairment may occur via multiple molecular pathways.

Here, we report a case of peno-scrotal lymphedema occurring after initiation of acalabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in an elderly patient who had a history of radical prostatectomy and pelvic lymphadenectomy. A narrative review was conducted to provide a comprehendsive and critical overview of the existing literature on tyrosine kinase inhibitors lymphatic side effects. Given that some lymphatic adverse events may remain unpublished, pharmacovigilance databases were also interrogated to assess potential signals related to tyrosine kinase inhibitors. This approach contributes to the understanding of potential functional impairment of lymphatic drainage by a TKI.

MATERIALS AND METHODS

Case report

Clinical, biological, and radiological data were retrospectively collected from the patient's medical record and clinical course was documented throughout management until the last follow-up. In accordance with French legislation, written consent is not required for non-interventional retrospective studies like case reports. Instead, the patient was informed and given the opportunity to opt out. The patient didn't express any objection and consented to publication. This study has been reported in line with the SCARE criteria (1).

Comprehensive literature review

Relevant literature was identified through targeted searches in PubMed. The search strategy combined keywords and subject headings related to tyrosine kinase inhibitors and lymphatic complications (*"chylothorax" OR "chylous ascites" OR "pericardial effusion" OR "protein-losing enteropathy" OR "chylous effusion" OR "chylous leak" OR "lymphedema"*) and was refined iteratively. Additional sources were identified through manual screening of reference lists and key journals.

Studies reporting lymphatic adverse events associated with TKIs were included regardless of publication date or study design, while non-relevant articles, animal studies, and papers not written in English or French were excluded. While formal quality assessment tools were not applied, each study was critically appraised for methodological soundness, clinical relevance, and clarity of reporting.

Pharmacovigilance data collection

To complement the literature review, the main international pharmacovigilance databases were queried in October 2025: FAERS (FDA (Food and Drug Administration) Adverse Event Reporting System), VigiAccess (World Health Organisation - WHO), and EudraVigilance (European Medicines Agency - EMA). Searches were performed using the drug name "acalabrutinib" and the MedDRA (Medical Dictionary for Regulatory Activities). reaction terms "lymphatic disorders" and "lymphedema." The number of reported cases for each term was recorded.

RESULTS

Case report

We report here the case of an 80-year-old

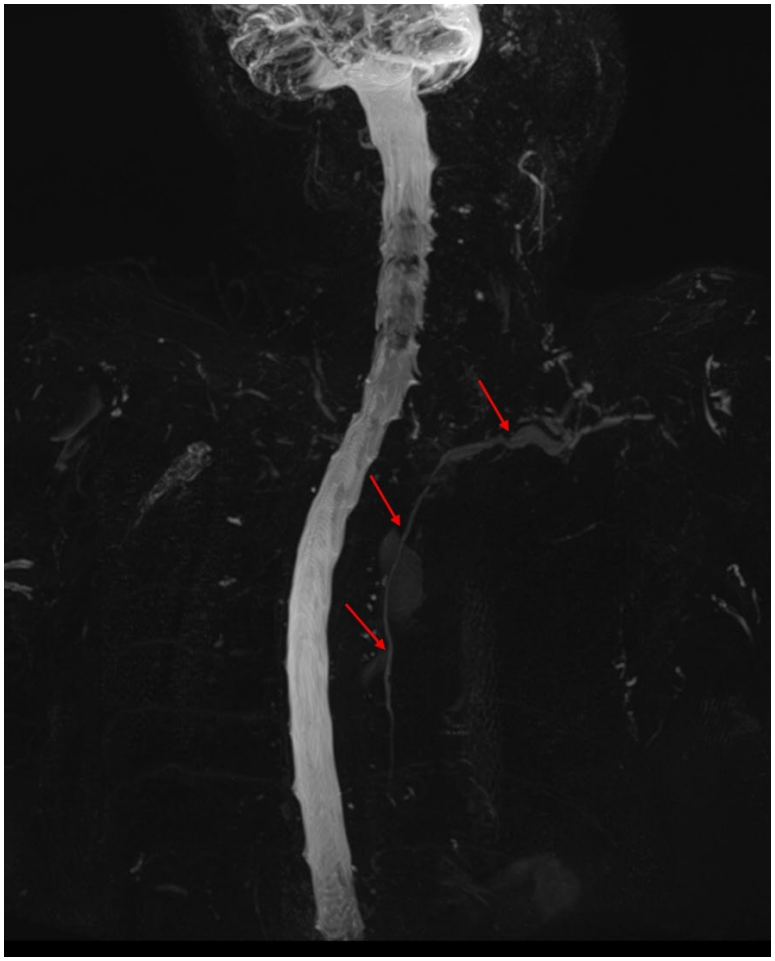

Fig. 1: *Lympho-MR image depicting a normal thoracic duct (arrows) with no dilatation and no morphologic anomalies.*

male patient who presented with peno-scrotal lymphedema which evolved over one year. Relevant medical history for the case included follow-up for chronic lymphocytic leukemia (CLL) since 2014 and prostatic adenocarcinoma in 2016. Preoperative imaging (MRI and choline-PET-CT) for treatment of the prostatic adenocarcinoma demonstrated multiple pelvic lymph nodes which may have been due to metastatic prostate cancer. Therefore, the patient underwent surgery consisting of radical prostatectomy plus extended (external iliac and ilio-obturator areas) lymph node dissection. The patient did not receive any other treatment (hormonotherapy, radiotherapy) pre or postoperatively. Postoperative period was marked by persistent lymphorrhea for which the abdominal drain was kept for five days. No peno-scrotal or lower-limb edema was observed during postoperative follow-up. The definitive histologic analysis retrieved an ISUP 2 prostatic adenocarcinoma, stage pT2cN0R0. Twenty-five lymph nodes were analyzed and demonstrated the known CLL.

For several years after surgery, the patient remained free of any clinical signs of lymphedema. Because of progression of CLL, acalabrutinib was introduced in November 2023. Within a few weeks after initiation of acalabrutinib, in February 2024, the patient

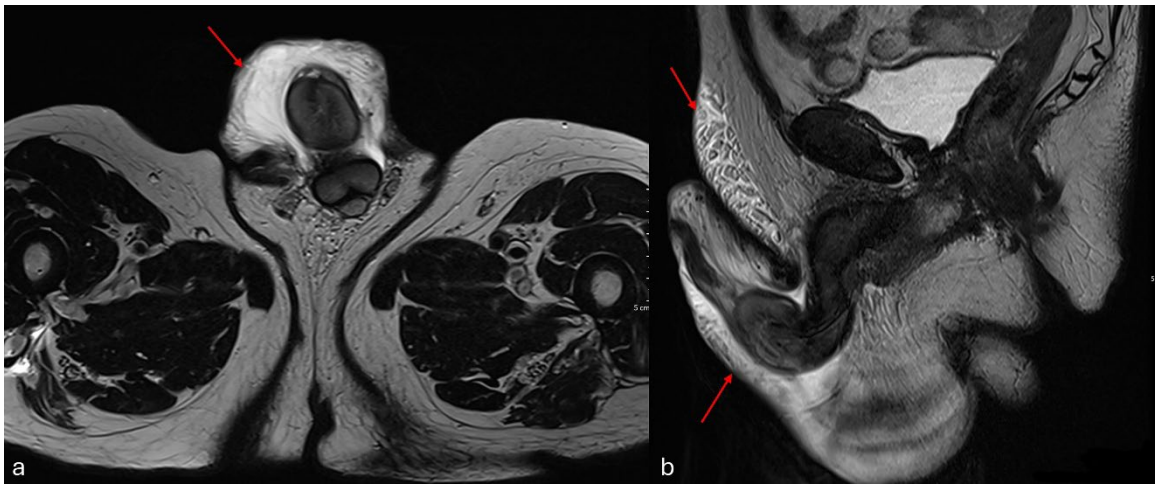

Fig. 2: *Axial (a) and sagittal (b) MR images demonstrating T2-weighted signal hyperintensity (arrows) consistent with subcutaneous edema and lymphatic stasis in the peno-scrotal region.*

reported a progressive development of peno-scrotal swelling, with no associated lower-limb edema. The initial workup included a cardiological assessment with echocardiography, which was unremarkable, and a Doppler ultrasound of the lower limbs, which showed no evidence of deep vein thrombosis or venous insufficiency. Malignant progression was investigated and excluded.

Given the persistence of edema, an exploration of the lymphatic system was undertaken. Morphological assessment was performed with magnetic resonance lymphography (MRL) without contrast injection, which showed normal abdominal lymphatic pathways without dilatation, including a thoracic duct of normal caliber up to its venous junction (*Fig. 1*). However, subcutaneous edema consistent with lymphatic congestion was noted at the peno-scrotal level (*Fig. 2*). Native MRL did not demonstrate macroscopic abnormalities of the pelvic lymphatic system, but is limited in its ability to assess lymphatic transport function. In the absence of any structural abnormality, a functional impairment of the lymphatic system was suspected.

Functional exploration was then performed using 4D-CT lymphangiography, combining CT imaging with a flat-panel detector for multimodal assessment: real-time fluoroscopy to evaluate lymphatic dynamics and intraoperative CT for precise three-dimensional anatomy. Under ultrasound guidance, superficial inguinal lymph nodes were punctured, and iodinated contrast agent was injected. After 20 minutes, no progression of the contrast agent into the abdominal or central lymphatic pathways was observed (*Fig. 3*). No lymphatic leak was detected. Lymphoscintigraphy was not performed.

Taken together, these findings suggested a functional lymphatic anomaly (acknowledging the potential morphological changes due to the prostatic adenocarcinoma treatment as seen in MRL congestion), which was considered consistent with a functional lymphatic impairment temporally associated with the initiation and continuance of acalabrutinib therapy. Considering the therapeutic benefit of acalabrutinib in chronic lymphocytic leukemia and the relatively limited impact of the lymphedema on the patient's quality of life, a decision was made to continue treatment with simple clinical follow-up.

Comprehensive literature review

The initial literature search (*Fig. 4*) retrieved 129 references, screened on the basis of title and abstract. Of these, 57 were identified

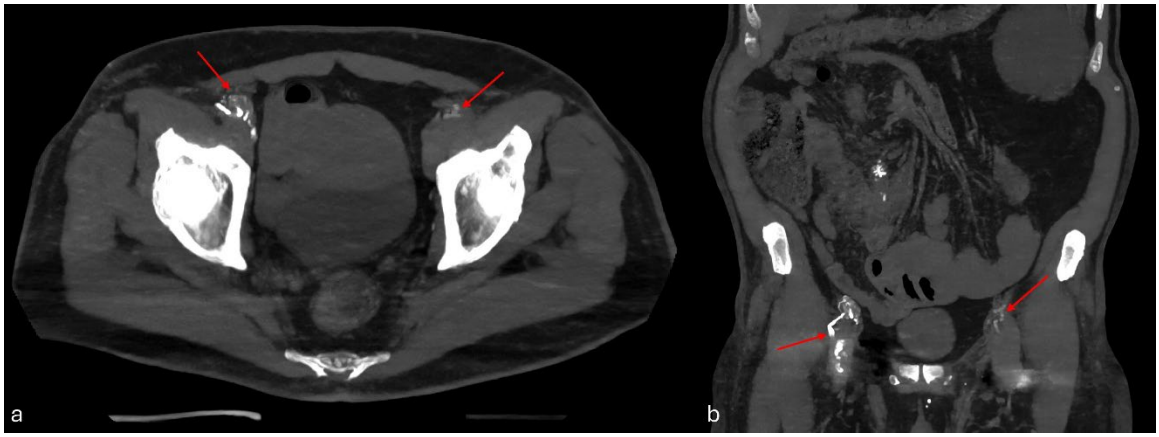

Fig. 3: *Abdominal CT following bi-inguinal lymphography injection showing opacification of the first nodal regions (arrows) without further transit into the abdominal lymphatic pathways.*

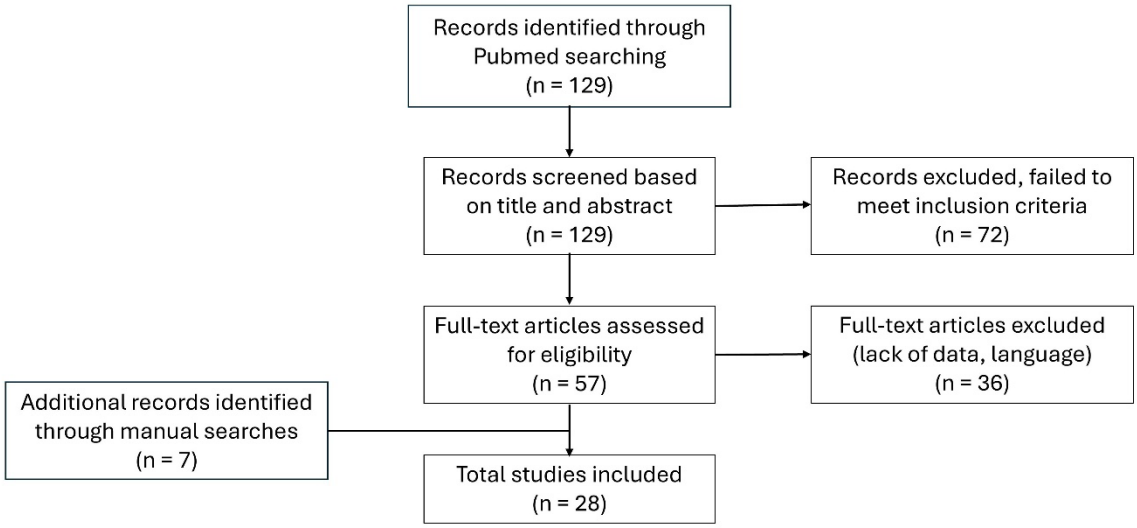

Fig. 4: *PRISMA-styled flow chart summarizing the literature search and selection process.*

as appropriate for full-text review. Finally, after full-text review and examination, 28 articles were included.

The literature review did not identify any case of lymphedema induced by tyrosine-kinase inhibitors. However, we identified 20 case reports dealing with TKI-induced chylothorax and these primarily involved the use of dasatinib (2–21). One case of bilateral chylothorax also occurred after treatment with alectinib (22), and one case was reported in association with bosutinib (23). The suggested etiology is that microscopic disruptions in lymphatic channels lead to chylous effusions following dasatinib (4). This effect seems to be specific in dasatinib therapy. A short literature review of case reports illustrates the management of dasatinib-induced chylothorax, often consisting in dasatinib discontinuation and switching to another therapy (19). This management resulted, in all cases, in chylothorax improvement.

TABLE 1
Pharmacovigilance Data on Lymphatic Adverse Events Associated with Acalabrutinib (Extracted from The Main Databases)

Database	Instance	Geographical scope	Lymphatic disorders	Lymphedema
VigiAccess	WHO	International	7	18
FAERS	FDA	USA	4	24
EudraVigilance	EMA	Europe	1	2

EMA: European Medicines Agency; FAERS: FDA Adverse Event Reporting System; FDA: Food and Drug Administration; USA: United States of America; WHO: World Health Organization.

The review also identified 4 cases of TKI-induced chylopericardium, 2 after imatinib treatment (24,25), one with dasatinib (26), and one with nilotinib (27), all improving after TKI discontinuation, and 2 cases of pleuropericardial effusion, one resolving after discontinuation (28), and the second one treated with diuretics (29).

The largest and most methodologically robust study identified by the review was a multicenter retrospective study of 7,517 patients treated by TKI, performed by Kalchiem-Dekel et al (30). In this study, chylous effusions occurred in 22 patients: 12 patients had chylothorax, five had chylous ascites, and five had both. These manifestations were most common with selpercatinib (7%), followed by agerafenib (4%), cabozantinib (0.3%), and lenvatinib (0.02%).

Moreover, a number of studies (not included in the review) including pharmacovigilance retrospective studies using Food and Drug Administration Adverse Event Reporting System (FAERS), identified tyrosine kinase inhibitors as frequent causes of pleuropericardial effusions, with no details about chylous nature or not (31–35).

Pharmacovigilance data

The pharmacovigilance search identified a limited number of lymphatic adverse events associated with acalabrutinib across the three main international databases (*Table 1*). Overall, 44 cases of lymphedema and 12 cases of lymphatic disorders were reported in pharmacovigilance databases. Most of them were reported in FAERS, while smaller numbers were found in VigiAccess and EudraVigilance. No clinical details were available in these spontaneous reports.

DISCUSSION

We present the case of an 80-year-old male patient with a peno-scrotal lymphedema potentially induced by acalabrutinib. The literature review did not identify any previous published case of TKI-induced lymphedema, making this case, to the best of our knowledge, the first published on the subject. Our review of the literature, however, identified several reports of TKI-related chylous effusions, most commonly associated with dasatinib, but also described with other agents such as alectinib, bosutinib, imatinib, and nilotinib. In addition, a large multicenter study (30) confirmed that chylous complications are not uncommon across different TKIs.

Furthermore, searches in international pharmacovigilance databases (FAERS, VigiAccess, and EudraVigilance) identified a limited number of lymphatic adverse events under acalabrutinib, including a few reports of lymphedema.

Pelvic lymph node dissection is a well-recognized cause of lymphatic injury and may lead to lymphatic insufficiency that can remain clinically silent for prolonged periods. In the present case, the absence of clinical lymphedema for several years after surgery strongly suggests that lymphatic compensation was

initially sufficient despite structural alteration of pelvic lymphatic pathways. The main hypothesis proposed to explain the mechanisms underlying these complications as suggested by most authors (4,30), is that microscopic alterations of lymphatic channels and impaired endothelial integrity lead to leakage of lymph. This is consistent across different TKIs, though the effect appears to be particularly marked with dasatinib. Under usual conditions, functional alterations of lymphatic drainage may be compensated by collateral pathways. In our patient, however, the history of prostatectomy with pelvic lymphadenectomy likely disrupted this collateral system leading to fluid accumulation in the peno-scrotal region and resulting in lymphedema. Although peno-scrotal lymphedema is clinically recognized as a potential complication of pelvic lymph node dissection (0-1% in published series (36)), published data specifically describing delayed-onset peno-scrotal lymphedema occurring years after surgery are scarce. Reported lymphatic complications related to pelvic lymphadenectomy typically occur in the early postoperative period, further supporting the role of an intercurrent triggering event in the present case.

This observation may contribute to a better pathophysiological understanding of Central Conducting Lymphatic Anomalies (CCLA). These rare conditions involve the thoracic duct and its major tributaries, and can present with diverse clinical manifestations related to chyle accumulation in different compartments, such as chylothorax, chylous ascites, chylopericardium, or lymphedema (37–39). The main hypothesis, based on individual observation but never statistically assessed (40–42), is that there are obstructive (43) and functional etiologies. Functional etiologies are characterized by impaired drainage without macroscopic obstruction. TKI-induced lymphatic adverse events appear to fall into this latter category, as they are most likely caused by microscopic disruptions of lymphatic integrity rather than by structural obstruction. Our patient's presentation therefore supports the concept of functional CCLAs and highlights the relevance of distinguishing between these two pathophysiological entities. This distinction is particularly important given the emergence of novel treatments like lymphovenous anastomosis (44) to treat obstructtive CCLA, which could probably be inefficient in functional CCLA. This highlights the need for a robust classification of CCLA.

Recent advances in molecular genetics have identified somatic mutations in RAS pathway genes in patients with CCLAs, providing a clear pathogenic basis for certain functional forms (37). Interestingly, this parallels the drug-induced lymphatic complications observed with TKIs, where impaired drainage results from acquired microscopic alterations of lymphatic integrity rather than congenital structural defects. Both mechanisms highlight the concept of functional lymphatic impairment, whether genetically determined or pharmacologically induced.

The specific contribution of Bruton's tyrosine kinase (BTK) to lymphatic biology remains poorly understood. BTK is predominantly expressed in hematopoietic cells, where it regulates B-cell receptor signaling and macrophage activation (45). Although direct evidence for a role in lymphatic vessel development or function is lacking, BTK inhibition could indirectly affect lymphatic homeostasis through modulation of immune-cell–derived cytokines and macrophage-driven lymphangiogenesis. This hypothesis remains speculative but warrants consideration given the known interplay between immune signaling and lymphatic endothelial integrity.

This case broadens the spectrum of lymphatic complications associated with TKIs and provides additional support for the functional versus obstructive paradigm in CCLAs. However, further clinical and preclinical studies are needed to better elucidate the mechanisms underlying functional lymphatic drainage impairment.

CONCLUSION

This case represents, to the best of our knowledge, the first report of TKI-induced lymphedema. However, one must be cognizant of the fact that our patient had a prior prostatectomy with pelvic lymphadenectomy that

likely impacted his lymphatic system- although no edema was present for years until the induction of acalabrutinib. Our findings broaden the spectrum of lymphatic complications associated with TKI agents and supports the concept of functional rather than obstructive impairment, as described in CCLA. Further clinical and preclinical studies are warranted to better characterize functional alterations of lymphatic drainage and in patients without prior lymphatic system insults.

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There is no funding source for this work.

CONFLICT OF INTEREST

All authors declare no competing financial interests exist

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication and any accompanying images.

ETHICAL APPROVAL

This case report does not require ethical approval as it involves a single patient case that is anonymized and does not include any identifiable personal information.

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ABBREVIATIONS

BTK: Bruton's Tyrosine Kinase
CCLA: Central Conducting Lymphatic Anomalies
CLL: Chronic Lymphocytic Leukemia
EMA: European Medicines Agency
FAERS: FDA Adverse Event Reporting System
FDA: Food and Drug Administration
MedDRA: Medical Dictionary for Regulatory Activities
TKI: Tyrosine-Kinase Inhibitor
USA: United States of America
WHO: World Health Organization

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