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Selpercatinib induced intestinal lymphangiectasia in RET fusion positive metastatic non-small cell lung cancer

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Abstract
RET (Rearranged during Transfection) is a transmembrane receptor protein-tyrosine kinase commonly associated with non-small cell lung adenocarcinomas, particularly those harboring RET fusion proteins [1]. Selective kinase inhibitors, such as Selpercatinib, have been developed to target RET tyrosine kinase receptors with higher specificity, aiming to improve treatment outcomes and reduce side effects compared to multitarget tyrosine kinase inhibitors [2]. Some of the side effects that have been reported with Selpercatinib are dry mouth, diarrhea, elevated liver enzymes, hypertension, prolonged corrected QT interval, fatigue/asthenia and abdominal pain [1]. While intestinal lymphangiectasia has been reported as a rare complication of multitarget tyrosine kinase inhibitors, to our knowledge, this is the first report of intestinal lymphangiectasia in a patient receiving the new generation of kinase inhibitors (Selpercatinib), which is considered a selective kinase inhibitor. We present the clinical presentation, diagnostic evaluation, and implications of this unique case. Due to the rarity of this complication and the presence of nonspecific symptoms, diagnosis can be difficult or delayed. Raising awareness about this rare complication can facilitate early diagnosis and improve care for cancer patients receiving Selpercatinib or similar targeted therapies.

Keywords: Kinase inhibitor, intestinal lymphangiectasia, selpercatinib

Introduction
Intestinal lymphangiectasia is a rare complication associated with the use of tyrosine kinase inhibitors (TKIs) in the treatment of various cancers, including non-small cell lung adenocarcinoma harboring RET fusion proteins. Multitarget tyrosine kinase inhibitors have been associated with a higher incidence of intestinal lymphangiectasia, prompting the development of selective kinase inhibitors like Selpercatinib. However, the occurrence of intestinal lymphangiectasia following treatment with Selpercatinib has not been previously reported.

Intestinal lymphangiectasia is characterized by the dilation of lymphatic vessels in the small intestine, leading to symptoms such as fatigue, weight loss, abdominal pain, nausea, and diarrhea. Diagnosis is typically based on clinical symptoms and imaging findings, including computed tomography (CT) scans demonstrating thickening, submucosal edema, or fat attenuation of the small bowel. In rare cases, biopsies may be performed to confirm the diagnosis by examining dilated lymphatic vessels in the lamina propria.

The rarity of intestinal lymphangiectasia as a complication of selective kinase inhibitors, along with its nonspecific symptoms, can pose challenges in diagnosis and potentially lead to delays in appropriate management. Raising awareness about this rare complication is crucial for early detection and improved care in cancer patients receiving Selpercatinib or similar targeted therapies. This report contributes to the existing knowledge on intestinal lymphangiectasia associated with kinase inhibitors, discussing its clinical presentation, diagnostic evaluation, and implications.

In this case report, we present the first known case of intestinal lymphangiectasia in a patient undergoing treatment with Selpercatinib. Our patient, a 56-year-old male with a history of lung adenocarcinoma and RET fusion, experienced loose bowel movements and fatigue within a month of starting Selpercatinib therapy. Serial CT scans performed over a period of three to sixteen months showed progressive jejunal wall thickening and submucosal fat attenuation.

Subsequent enteroscopy and pathology examination confirmed the diagnosis of intestinal lymphangiectasia, highlighting the importance of biopsy confirmation in such cases.

Case presentation

We present the case of a 56-year-old male patient with a medical history of type 2 diabetes, essential hypertension, and gastroesophageal reflux disease (GERD), who was diagnosed with lung adenocarcinoma. The patient underwent left upper lobectomy for biopsy-proven cT1bN0M0 lung adenocarcinoma. Two years later, he was diagnosed with metastatic hilar adenopathy from the primary lung adenocarcinoma and tested positive for RET fusion. Selpercatinib was prescribed at a dosage of 160 mg twice a day. Within a month of starting Selpercatinib, the patient developed loose bowel movements and fatigue. Serial CT scans performed between three to sixteen months after initiating Selpercatinib treatment showed progressive jejunal wall thickening and submucosal fat attenuation (Figure 1). Subsequently, an enteroscopy was performed sixteen months after treatment initiation, demonstrating nonspecific changes. Pathology examination of the random biopsies showed focal inflammation and dilated vessels in the small intestinal mucosa. Immunohistochemical stains demonstrated dilated lymphatic vessels in the lamina propria, as highlighted by D2-40 and CD34; consistent with lymphangiectasia (Figure 2). The patient provided informed consent for the publication of his information.

Discussion

Intestinal lymphangiectasia is a rare and unique side effect observed with tyrosine kinase inhibitors (TKIs). Previous studies have reported a significantly higher incidence of intestinal lymphangiectasia in patients receiving multitarget tyrosine kinase inhibitors, such as pazopanib, sunitinib, and cabozantinib, compared to single-target tyrosine kinase inhibitors like afatinib and osimertinib [3]. The small intestine is reported to be more commonly involved followed by the large intestine (71% and 43% respectively) [3]. Diagnosis is usually based on clinical symptoms and cross-sectional imaging findings [3]. Rarely, these patients may also undergo biopsy, which confirms the diagnosis. Typical clinical symptoms include fatigue, weight loss, abdominal pain, nausea, and diarrhea. Abdominal CT scans may reveal diffuse thickening, submucosal edema, or fat attenuation of the small bowel. On microscopic examination dilated lymphatic vessels are seen in the lamina propria region of the villous structure which may extend into the submucosa [4].

Reducing the dosage or discontinuing the treatment can alleviate the symptoms, and subsequent CT scans often demonstrate a reduction in submucosal fat thickness [3].

Most of the intestinal lymphangiectasia cases have been reported with multi-target TKI [3 5]. For example, Awiwi & Naik (2022) reported a case of intestinal lymphangiectasia in a 27-year-old female patient with renal cell carcinoma within a year of undergoing treatment with Cabozantinib [3]. Similarly, Masui *et al* (2022) reported a 62-year-old male patient diagnosed with renal cell carcinoma with metastasis that developed intestinal lymphangiectasia four years after starting treatment with Pazopanib [5]. TKIs have also been reported to cause dermal lympgangiectasia [6], upper eyelid lymphangiectasia [7] and chylothorax [8].

A study conducted by Tamir *et al* (2021) found multi target TKIs caused submucosal fat attenuation in the gastro-intestinal tract on CT scans in a significant proportion of their patients compared to those treated with single target TKIs who did not develop any [9]. They presumed these findings were due to intestinal lymphangiectasia secondary to mt-TKI usage. However, the study lacked pathology confirmation.

Similarly, our patient developed symptoms of loose bowel movements and fatigue within a month of starting treatment. While the patient's symptoms were mild and dose reduction or complete cessation of treatment was not perused, however, serial CT images through a span of 3-16 months demonstrated progressive worsening of wall thickening and submucosal edema/fat attenuation of the jejunal folds, which was the only organ involved in our case. While most of the prior studies, including the study by Tamir *et al* [9], have relied on clinical and imaging features for the diagnosis, our study is among the very few where diagnosis of iatrogenic intestinal lymphangiectasia was confirmed by pathology.

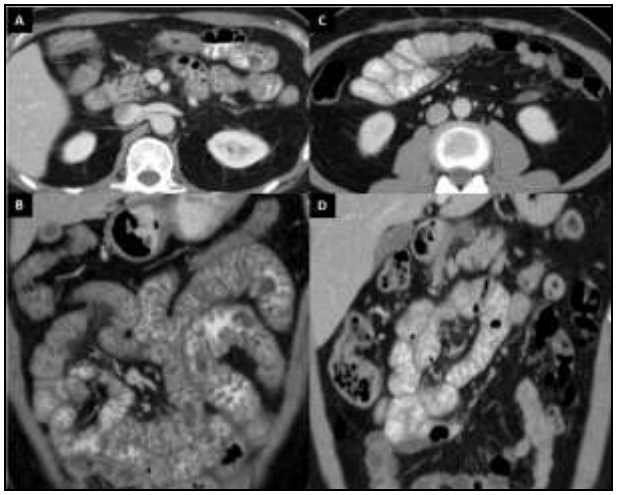

Fig 1: Axial (A) and coronal (B) images of the abdomen obtained after starting treatment with Selpercatinib demonstrate small bowel wall thickening with low-attenuation thickening of the jejunal plicae circularis, which is new compared to pre-treatment axial (C) and coronal (D) CT images.

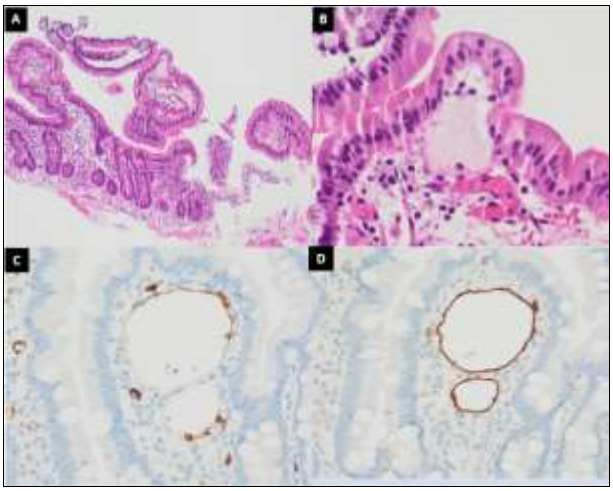

Fig 2: A & B, the jejunal biopsy shows nonspecific chronic inflammation and dilated vessels in the intestinal mucosa (A, H&E, x10; B, H&E, x40). Immunohistochemical stains showed rare dilated lymphatic vessels in lamina propria, as highlighted by CD34 (B) and D2-40 (C). The CD34 immunostaining also highlighted blood vessels.

Table 1: Summary of Previous Case Reports of Tyrosine Kinase Inhibitors (mt-TKIs) Developing Lymphangiectasia and Lymphatic Vessel Complication

References	Age (year)	Sex	Type of Disease	Treatment	Complication	Time since treatment onset
Awiwi et al[3]	27	F	RCC with metatstasis	cabozantinib	intestinal lymphangiectasia	1 year
Tamir et al[9]	34-83	M	RCC	pazopanib or sunitinib	intestinal lymphangiectasia	within 2 years
Masui et al[5]	62	M	RCC with metatstasis	pazopanib	intestinal lymphangiectasia	4 years
Weber et al[6]	32	F	ALL involving the Central nervous system	methotrexate, cytarabine, and ponatinib	dermal lymphangiectasia	5 weeks
McClelland et al[7]	64	F	CML	Imatinib	Upper eyelid Lymphangiectasia	within few weeks of increasing dose
Hickman et al[8]	5	F	CML	dasatinib	Chylothorax	10 months

RCC: renal cell carcinoma; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia.

Conclusions

Intestinal lymphangiectasia is a rare complication associated with tyrosine kinase inhibitors. Selective kinase inhibitors, such as Selpercatinib, have been developed to overcome the side effects of nonselective multitarget tyrosine kinase inhibitors. To our knowledge, this is the first report of intestinal lymphangiectasia after treatment with Selpercatinib. Due to the nonspecific symptoms of intestinal lymphangiectasia, screening suspected patients using imaging studies in conjunction with intestinal biopsies can help confirm the diagnosis. Raising awareness about this rare complication is crucial for early detection and improved care in cancer patients receiving Selpercatinib or similar targeted therapies.

Conflicts of Interest

The authors declare no conflict of interest.

Informed Consent

The authors declare that written informed consent was obtained from the patient.

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