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【 CASE REPORT 】

# Successful Treatment of *ROS1*-rearranged Lung Cancer Complicated by Hypertrophic Pulmonary Osteoarthropathy with Crizotinib Therapy

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**Abstract:**

Hypertrophic pulmonary osteoarthropathy (HPO) is a paraneoplastic syndrome characterized by digital clubbing, arthritis, and periostitis. Tumor removal usually leads to the resolution of these symptoms. We herein report the efficacy of crizotinib treatment for treating the symptoms of HPO associated with c-ros oncogene 1 receptor tyrosine kinase (*ROS1*)-rearranged lung cancer. A 71-year-old woman presented with a pulmonary tumor and arthritis. She was diagnosed with a *ROS1*-rearranged lung adenocarcinoma [stage IIIB (cT 4N2M0)] with HPO. Crizotinib dramatically reduced the tumor size and resolved the symptoms. After two months of crizotinib treatment, she underwent lobectomy, and a pathological evaluation revealed ypstage IIIA (ypT3a, ypN1). Crizotinib treatment was effective for reducing the tumor size and improving the symptoms of HPO.

**Key words:** hypertrophic pulmonary osteoarthropathy, crizotinib, paraneoplastic syndrome, *ROS1*-rearranged lung cancer

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## Introduction

Hypertrophic pulmonary osteoarthropathy (HPO) is a rare paraneoplastic syndrome characterized by digital clubbing, arthritis, and periostosis of the tubular bones (1). Surgical resection of the primary tumor usually leads to the resolution of these symptoms. Surgical treatment leads to the improvement of HPO in 91.1-100% of cases (1, 2). Without surgery the improvement of HPO is only observed 60.0-77.4% of cases (1, 2). We herein report the case in which crizotinib treatment was significantly beneficial in the treatment of a patient with HPO associated with c-ros oncogene 1 receptor tyrosine kinase (*ROS1*)-rearranged lung cancer.

## Case Report

A 71-year-old woman was referred to our hospital with a tumor shadow in the right-upper lung field. She had experienced cough and painful edema in both lower extremities since the previous month. She had never smoked and had no history of any serious illness or familial history of hypertrophic osteoarthropathy. Her vital signs were normal. Chest auscultation and a general physical examination revealed decreased breath sounds in the right-upper lung field, digital clubbing of the fingers and toes, painful edema of both lower extremities, and bilateral swelling of the wrists and knees (Fig. 1A and B). The laboratory data showed leukocytosis (10,700 cells/μL) and elevated levels of C-reactive protein (7.48 mg/dL: reference range, <0.14 mg/dL), alka-

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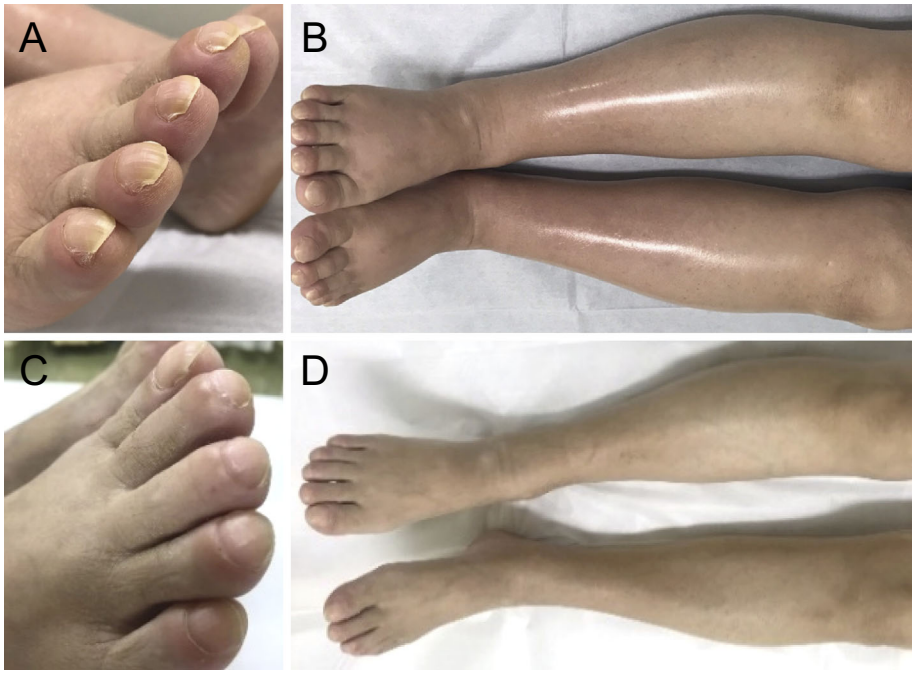


**Figure 1.** **(A, B) A physical examination revealed digital clubbing of the fingers and toes, with painful edema of the bilateral lower extremities. (C, D) The physical findings showed significant improvement after two months of crizotinib treatment.**

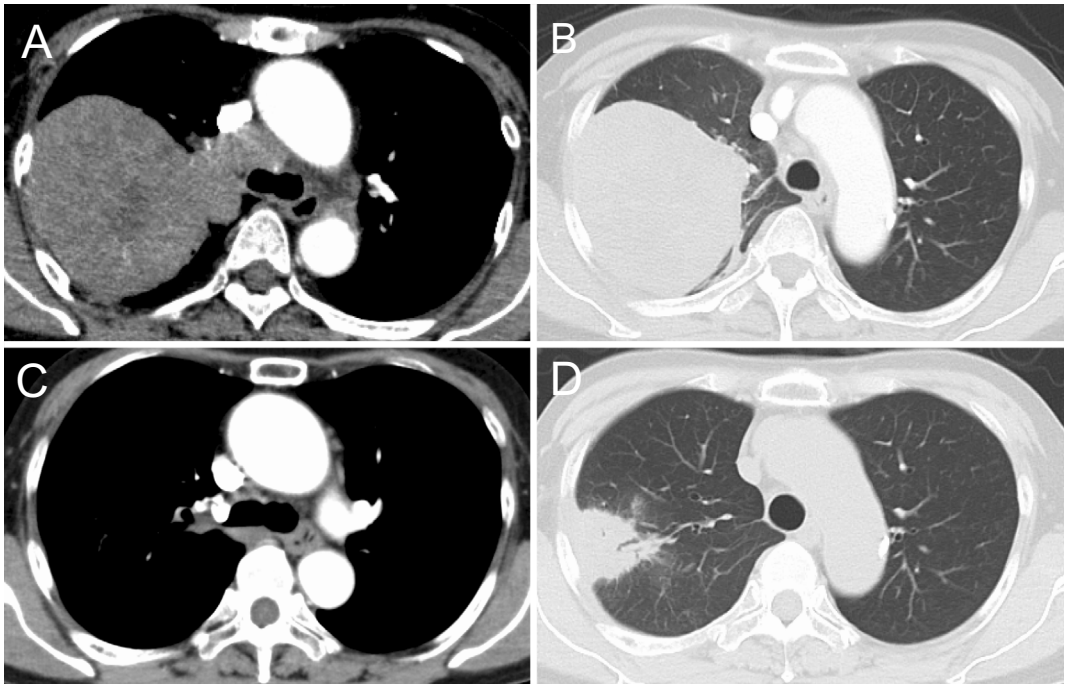


**Figure 2.** **(A, B) Computed tomography revealed a tumor measuring 90 mm in size in the right-upper lobe with hilar and mediastinal lymphadenopathy. (C, D) The tumor was decreased in size after two months of crizotinib treatment.**

line phosphatase (626 IU/L : reference range, <322 U/L), and vascular endothelial growth factor (VEGF) (271 pg/mL; reference range, <38.3 pg/mL). Computed tomography (CT) revealed a tumor measuring 90 mm in the right upper lobe, with hilar and mediastinal lymphadenopathy (Fig. 2A and B). Positron emission tomography-CT showed increased the uptake of fluorodeoxyglucose (FDG) by the tumor in the right-upper lobe and by the hilar and mediastinal lymph nodes. There was no uptake of FDG in other sites. Bone scintigraphy with Technetium-99m revealed bilateral uptake in the tibias, femurs, knees, and ankles (Fig. 3). A histopathological examination of a transbronchial

lung biopsy specimen showed adenocarcinoma. *ROS1* rearrangement was detected by a reverse transcriptase-polymerase chain reaction (RT-PCR). She was diagnosed with *ROS1*-rearranged lung adenocarcinoma [stage IIIB (cT4 N2M0)] with HPO.

She received crizotinib (250 mg twice a day). The arthralgia and edema in the lower extremities improved 4 days after the initiation of crizotinib treatment. After 2 weeks of crizotinib treatment, the tumor decreased to 48 mm in size. After two months, the tumor and the mediastinal lymph nodes were further reduced in size (Fig. 2C and D). In terms of the physical findings, there was an almost complete improvement (Fig. 1C and D). The level of VEGF was decreased to 115 pg/mL. With the decrease in tumor size, right-upper lobectomy and bronchoplasty with combined excision of the third and fourth ribs was performed in order to achieve complete resection. The tumor measured 32×33×45 mm, and a pathological evaluation revealed papillary adenocarcinoma, ypStage IIIA (ypT3a, ypN1) (Fig. 4A). The resection margins were negative. Residual-viable malignant cells were identified in less than one-third of all of the cells within the tumor. There were no malignant cells in the mediastinal lymph nodes. Immunohistochemistry revealed that the tumor was positive for ROS1 (Fig. 4B). At 3 months after surgery, the level of VEGF was found to have increased to 181 pg/mL, without obvious recurrence of cancer or HPO syndrome. There was no evidence of recurrence at a 4-month follow-up examination, despite the patient not receiving adjuvant chemotherapy.

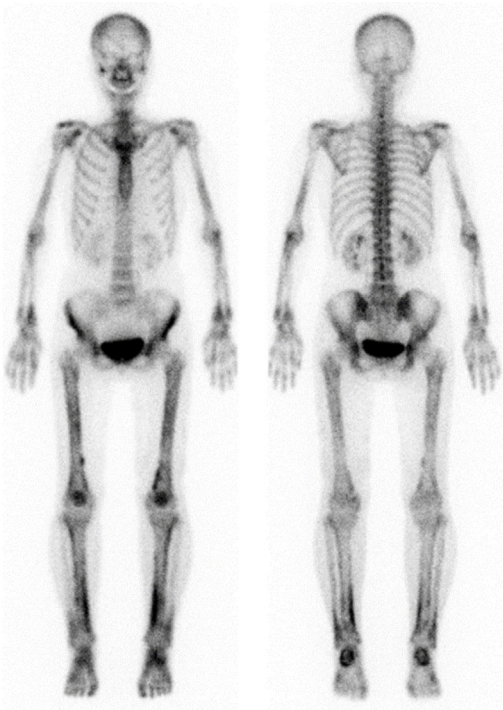

**Figure 3. Bone scintigraphy with $^{99m}$Tc complexes showed a symmetrical bilateral-linear uptake in the long bones.**

## Discussion

In this case, HPO was a complication of *ROS1*-rearranged lung cancer. Crizotinib dramatically resolved her symptoms and led to a reduction in the tumor size. To the best of our knowledge, this is the first case report of HPO associated with *ROS1*-rearranged lung cancer.

HPO is a rare condition that can accompany pulmonary disease. The incidence of HPO among lung cancer patients is 0.72-1.87% (1, 2). Bone scintigraphy typically shows a symmetrically increased uptake along the cortical margins in the distal long bones and the joints of the extremities (3). The pathogenesis of HPO has not been clearly identified, but biochemical, mechanical, and neurogenic mechanisms have been proposed (1). Previous studies have demonstrated the abnormal production of hypoxia-induced biochemical products including platelet-derived growth factor (PDGF), prostaglandin E2 (PGE2), and VEGF in patients with HPO (1, 4). In our patient, the VEGF level was elevated before treatment and decreased after the improvement of the patient's HPO-associated symptoms. However, the VEGF

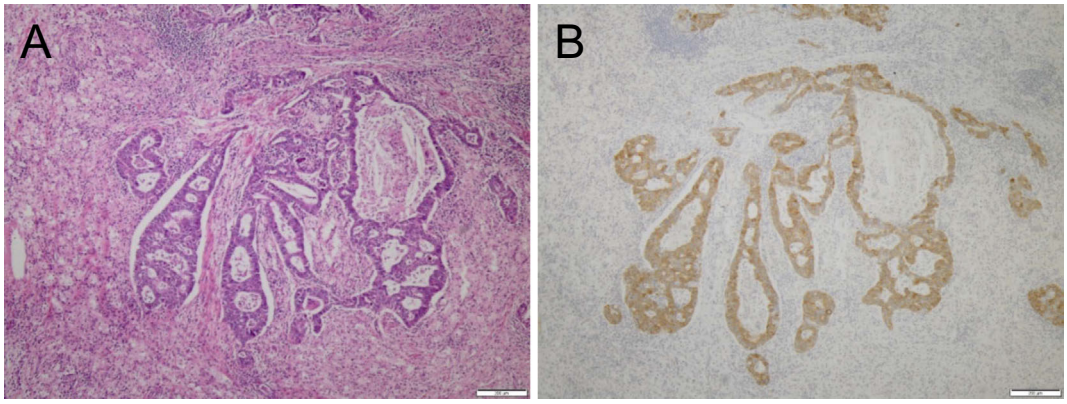


**Figure 4. Histopathology and immunohistochemistry of the tumor (4×). Scale bar indicates 200 μm. (A) Hematoxylin and Eosin staining of the tumor demonstrated papillary adenocarcinoma. Less than one-third of all of the cells within the tumor were viable malignant cells. (B) Immunohistochemistry demonstrated that the tumor cells were positive for ROS1.**

level increased again at 3 months after surgery. In general, VEGF is produced by endothelial cells, stromal cells, macrophages, and tumor cells. In this case, the VEGF level decreased due to the volume reduction associated with cancer treatment. Thus, the elevation of VEGF at 3 months after surgery may suggest the need to pay attention to the possibility of recurrence.

The common clinical characteristics of lung cancer patients with HPO are male sex, smoking history, adenocarcinoma, and advanced disease (1, 2, 5). It is unclear whether a driver oncogene is associated with the development of HPO in lung cancer patients, and there have been no previous reports of patient with *ROS1*-rearranged lung cancer complicated by HPO. A previous study showed that the proportion of epidermal growth factor receptor (*EGFR*)-positive cases among patients with HPO was extremely low (5). We are working on new project to survey the blood VEGF level and the expression of VEGF on the tumor tissue in patients with *EGFR*-mutated lung cancer.

The best treatment for HPO is resection of the primary tumor. It is well-known that HPO improves promptly after the removal of the underlying tumor (6). Molecular-targeted therapies are associated with a good response rate in lung cancer with oncogenic driver mutations (7). A few case reports have shown that targeted therapies are effective for improving the symptoms associated with HPO in patients with oncogenic driver mutations (8, 9). A previous report showed that treatment with gefitinib, an EGFR-TKI, dramatically improved the symptoms of HPO as well as primary lung lesions (8). *ROS1* rearrangement has been identified in approximately 1% of patients with non-small cell lung cancer (10). Crizotinib is an inhibitor of anaplastic lymphoma kinase, mesenchymal-epithelial transition (c-MET)/hepatocyte growth factor (HGF) receptor, and ROS1 receptor kinases. It is highly effective in the treatment of patients with *ROS1*-rearranged lung cancer, with an objective response rate of 72% (11). In this case, crizotinib promptly reduced the symptoms associated with HPO. As described above, HPO may be a consequence of hypoxia-induced mediators in tumor tissue, among other mechanisms. A previous report showed that crizotinib improved the symptoms of osteoarthritis (OA) in a patient with *ROS1*-rearranged lung cancer whose OA symptoms did not improve with cytotoxic chemotherapy. The authors suggested a molecular role of crizotinib through the downregulation of VEGF via a c-MET pathway, which led to the improvement of the OA symptoms (12). Another report showed that anti-VEGF agent (bevacizumab) reduced the plasma VEGF levels to within the reference range and led to the complete resolution of hypertrophic osteoarthropathy (HOA) symptoms despite failing to reduce the tumor size (13). In this case as well, the inhibition of MET signaling by crizotinib may have contributed to the reduction of the symptoms associated with HPO.

In this report, our patient underwent complete tumor resection two months after the administration of crizotinib therapy. There are limited data showing the efficacy of preoperative molecular-targeted therapies in patients with oncogenic mutations. Several case reports and clinical trials with a small sample size have shown the advantage of using preoperative molecular targeted therapies (14). Some of the reports suggested that neoadjuvant therapy contributed to tumor downstaging (15). Several prospective studies investigating the efficacy of preoperative molecular-targeted therapies in patients with *EGFR*-mutant lung cancer are currently underway (14).

## Conclusion

We describe a rare case in which crizotinib treatment led to the dramatic improvement of HPO symptoms that were associated with *ROS1*-rearranged lung cancer. It is important to control primary disease in patients with HPO. Crizotinib significantly reduced the tumor size, improved the symptoms of HPO, and facilitated the complete resection of a locally advanced lung cancer. Oncogene targeted-therapies, including crizotinib, can be effective treatments for advanced lung cancer complicated by HPO.

**The authors state that they have no Conflict of Interest (COI).**

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