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CASE REPORT

Rapidly Destructive Coxarthrosis as a Potential Side Effect of Crizotinib in a Patient with *ROS1*-Positive Lung Adenocarcinoma

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Abstract: A 75-year-old woman was diagnosed with *c-ros oncogene 1* (*ROS1*)-positive lung adenocarcinoma. She was treated with crizotinib 750 mg/day for 4.5 years, with partial tumor response. However, the patient subsequently presented with right hip pain and difficulty in walking. She underwent magnetic resonance imaging (MRI), which detected T2 prolongation in the right femoral bone head, synovial fluid retention, and bone joint fissure narrowing. The patient was diagnosed with rapidly destructive coxarthrosis (RDC) and received a total hip arthroplasty. This represents a rare case of RDC as a potential side effect of crizotinib in a patient with *ROS1*-positive lung adenocarcinoma. MRI should therefore be recommended in patients receiving crizotinib who experience continuing severe hip pain and difficulty in walking. Further investigations are warranted to elucidate the pathogenesis of RDC associated with crizotinib treatment.

Keywords: non-small cell lung cancer, *ROS1*, crizotinib, rapidly destructive coxarthrosis

Background

The *c-ros oncogene 1* (*ROS1*) was first described as a driver gene alteration in non-small cell lung cancer (NSCLC) in 2007,[1] and its rearrangement is detected in 1–2% of patients with NSCLC.[2] The first-generation tyrosine kinase inhibitor crizotinib demonstrated antiproliferative activity against *ROS1*-translocated NSCLC in vitro,[3] and a clinical study of crizotinib in patients with advanced *ROS1*-rearranged NSCLC showed an objective response rate of 72% and median progression-free survival of 19.2 months.[4] Based on these data, the US Food and Drug Administration approved crizotinib as the first targeted drug for patients with *ROS1*-rearranged NSCLC in March 2016. The most common reported side effects of crizotinib are gastrointestinal disturbances (diarrhea, nausea, constipation, and vomiting), visual impairment, and peripheral edema.[4,5] However, no treatment-related grade four or five adverse events have been reported,[4,5] suggesting that the side effects of crizotinib are tolerable.

Rapidly destructive coxarthrosis (RDC) is a rare syndrome characterized by progressive narrowing of the joint space and rapid joint destruction within 6–12 months, first reported by Postel et al in 1970.[6] Although total hip arthroplasty has been established for the treatment of RDC of a hip joint, the definitive etiology of RDC remains unclear.[6] Previous studies have suggested that several drugs, including steroids and anti-inflammatory agents, may be risk factors for the development

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of RDC.[7] However, to the best of our knowledge, no previous reports have suggested an association between RDC and molecular targeted drugs. We here present a rare case of RDC as a potential side effect of crizotinib in a patient with *ROS1*-positive lung adenocarcinoma.

Case Presentation

A 75-year-old woman presented with shortness of breath and was referred to a hospital. She was a never-smoker and had no significant abnormalities on physical examination. Chest computed tomography (CT) revealed pleural nodules and a mass in the right middle lobe. She underwent incisional biopsy of the pleural nodule by video-assisted thoracoscopic surgery under general anesthesia in 2010, and was diagnosed with primary lung adenocarcinoma (cT2aN1M1a, cStage IVA). She was administered cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2, and bevacizumab 15 mg/kg on day 1 every 3 weeks for five cycles. However, the patient attended the hospital but rejected further treatment. In 2011, blood examination showed elevated carcinoembryonic antigen, and 18-fluorodeoxyglucose positron emission tomography showed right pleural dissemination. She received pemetrexed 500 mg/m^2 and bevacizumab 15 mg/kg on day 1 every 3 weeks for six cycles, but chest CT revealed increased right pleural effusion. In 2012, the patient was administered docetaxel (60 mg/m^2) for three cycles as second-line chemotherapy, but this was discontinued due to an allergic response. Chest CT in May 2013 revealed increased right pleural effusion and the patient underwent right thoracic drainage. The pleural effusion was submitted for examination of driver genes, and was shown to be positive for *ROS1*. The patient participated in a clinical trial and was administered crizotinib 750 mg/day as third-line therapy from December 2013. The tumor showed partial response to crizotinib therapy for approximately 4.5 years. In April 2018, the patient presented with right hip pain and difficulty in walking, and was referred to our hospital. A chest X-ray imaging showed slight deformation of the right femoral bone head and bone joint fissure narrowing (Figure 1A). Magnetic resonance imaging (MRI) detected T2 prolongation in the right femoral bone head, synovial fluid retention, and bone joint fissure narrowing (Figure 1B). These findings were not observed in the previous roentgenological imaging five months ago. We consulted an orthopedic specialist, and the patient was clinically diagnosed with right RDC. She underwent a total hip arthroplasty at another hospital in May 2018. Pathological examination showed bone tissue with osteonecrosis, fat necrosis, debris, and granulation tissue in the medullary spaces. No specific inflammation or malignancy was observed, and the pathological diagnosis was aseptic necrosis, rather than bone metastasis. Because the patient had received no other suspected drugs, including

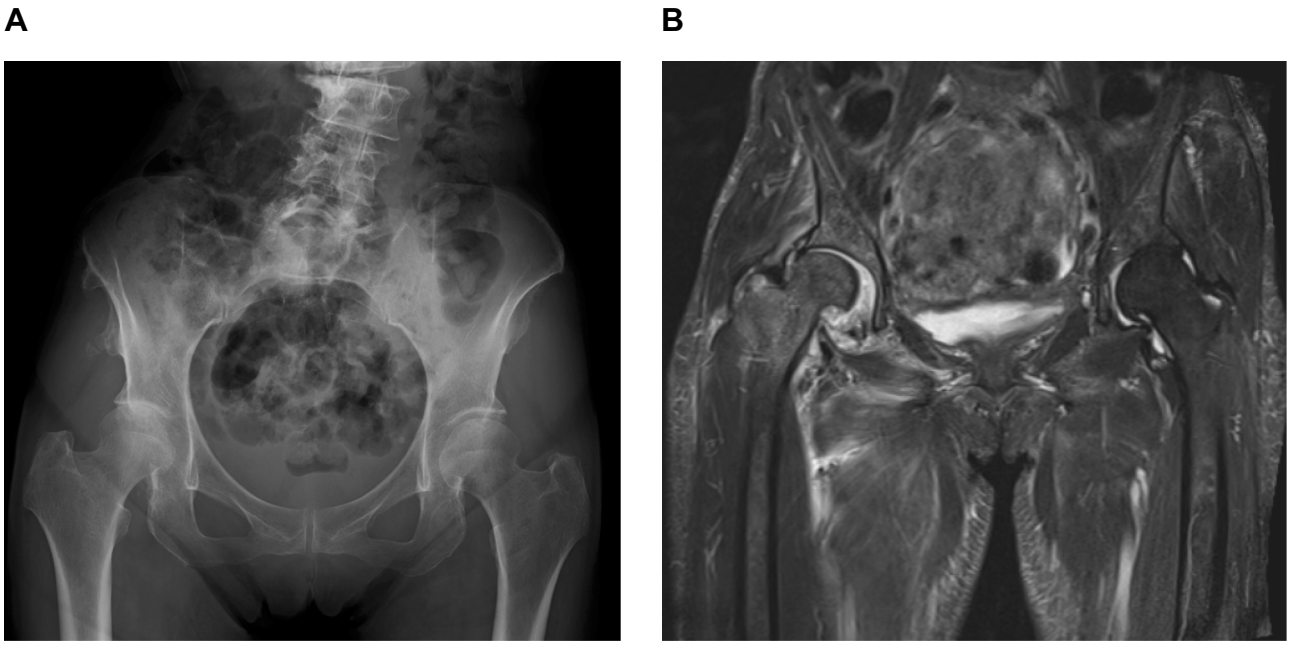

Figure 1 (**A**) A chest X-ray imaging showed slight deformation of the right femoral bone head and bone joint fissure narrowing. (**B**) Magnetic resonance imaging detected T2 prolongation in the right femoral bone head, synovial fluid retention, and bone joint fissure narrowing. These findings were not observed in the previous roentgenological imaging five months ago. The patient was diagnosed with right rapidly destructive coxarthrosis as a side effect of crizotinib.

steroids or anti-inflammatory agents, the clinical trial office in our hospital judged the RDC to be a severe adverse event induced by crizotinib. The patient's hip pain resolved rapidly after surgery, and crizotinib was resumed in June 2018. The latest chest CT in November 2018 revealed partial tumor response.

Discussion

Crizotinib is a first-generation tyrosine kinase inhibitor with antiproliferative activity against *ROS1*-translocated NSCLC.[3] Previous clinical trials investigating the efficacy and safety of crizotinib in patients with *ROS1*-rearranged NSCLC reported visual impairment, diarrhea, nausea, peripheral edema, constipation, and vomiting as side effects, but no treatment-related grade four or five adverse events.[4,5] Phase I–III clinical trials of crizotinib in patients with anaplastic lymphoma kinase (*ALK*)-positive NSCLC showed a similar safety profile of crizotinib to that in patients with *ROS1*-positive NSCLC.[8] The lack of severe crizotinib-related adverse events in previous clinical trials suggest that the occurrence of crizotinib-induced RDC with serious symptoms (hip pain and difficulty in walking) in this patient with *ROS1*-positive lung adenocarcinoma represents a very rare case.

The etiology and causes of RDC remain unclear.[6] Several studies have indicated that some drugs, including steroids and anti-inflammatory drugs, may cause RDC.[7] However, there have been no reports of RDC induced by anticancer agents. To the best of our knowledge, the current case represents the first report of a potential association between a molecular targeted drug and RDC. The possible causal relationship between crizotinib and RDC is unknown. Crizotinib inhibits the hepatocyte growth factor (HGF) receptor c-MET and downregulates the HGF-MET signaling axis.[1] HGF and c-MET mRNA were reported to be upregulated in synovial tissue in rheumatoid arthritis and osteoarthritis.[9] HGF binds to c-MET on endothelial cells and induces angiogenesis, which may be associated with bone and joint destruction in RDC.[10] However, these previous studies suggest that crizotinib should inhibit, rather than induce, the pathogenesis of RDC, and do not indicate a link between crizotinib and the mechanisms underlying RDC. Further detailed analyses of the synovial fluid and/or membrane may help to clarify the etiology of RDC in relation to crizotinib treatment.

The current report is associated with a limitation. According to the previous reports, RDC of the hip is an idiopathic rare disease usually seen in older women of 70 to 80 years old, and is typically unilateral.[6] Given that the current case is a 74-year-old female with right-sided unilateral RDC, idiopathic RDC cannot be excluded from the differential diagnosis.

In conclusion, we present a case of crizotinib-induced RDC of a hip joint in a patient with *ROS1*-positive lung adenocarcinoma. We recommend MRI in patients administered crizotinib who experience continuing severe hip pain and difficulty in walking. Further investigations are warranted to elucidate the pathogenesis of RDC as a possible side effect of crizotinib.

Ethics

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

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell*. 2007;131:1190–1203. doi:10.1016/j.cell.2007.11.025
2. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30:863–870. doi:10.1200/JCO.2011.35.6345
3. Yasuda H, de Figueiredo-pontes LL, Kobayashi S, Costa DB. Preclinical rationale for use of the clinically available multitargeted tyrosine kinase inhibitor crizotinib in ROS1-translocated lung cancer. *J Thorac Oncol*. 2012;7:1086–1090. doi:10.1097/JTO.0b013e3182570919
4. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371:1963–1971. doi:10.1056/NEJMoa1406766
5. Wu YL, Yang JC, Kim DW, et al. Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36:1405–1411. doi:10.1200/JCO.2017.75.5587
6. Postel M, Kerboull M. Total prosthetic replacement in rapidly destructive arthrosis of the hip joint. *Clinical Orthopaedics and Related Research*. 1970;72:138–144.
7. Yoshino K, Momohara S, Ikari K, et al. Acute destruction of the hip joints and rapid resorption of femoral head in patients with rheumatoid arthritis. *Mod Rheumatol*. 2006;16:395–400. doi:10.3109/s10165-006-0516-0
8. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a Phase 1 study. *Lancet Oncol*. 2012;13:1011–1019. doi:10.1016/S1470-2045(12)70344-3

9. Guevremont M, Martel-Pelletier J, Massicotte F, et al. Human adult chondrocytes express hepatocyte growth factor (HGF) isoforms but not HgF: potential implication of osteoblasts on the presence of HGF in cartilage. *J Bone Miner Res*. 2003;18:1073–1081. doi:10.1359/jbmr.2003.18.6.1073

10. Yamakawa T, Sudo A, Tanaka M, Uchida A. Microvascular density of rapidly destructive arthropathy of the hip joint. *J Orthop Surg (Hong Kong)*. 2005;13:40–45. doi:10.1177/230949900501300107