Advanced Secondary Lung Adenocarcinoma, ALK Mutation, from Treatment of Childhood Osteopetrosis: Case Report

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Abstract

A 28-year-old male with a childhood history of osteopetrosis treated with a stem cell transplantation (SCT) presented with chronic fatigue, malaise, and abdominal pain. CT imaging identified a left lung nodule with osseous, hepatic, and splenic metastases, and diffuse lymphadenopathy. Hepatic biopsy demonstrated metastatic pulmonary adenocarcinoma, ALK-mutated. He received alectinib with an excellent radiographic response maintained a year later. Recipients of a SCT have an increased risk of secondary solid cancer (SSC) and a cumulative incidence of 10-15% by 15-years. Awareness and screening for SSCs are essential for an earlier diagnosis and the possibility of improved outcomes.

Introduction

Infantile malignant osteopetrosis (IMO) is a rare and fatal autosomal recessive disorder with an incidence of 1/250,000. IMO is caused by osteoclast dysfunction, leading to increased bone density, and hematopoietic insufficiency[1]. Classic IMO is characterized by short stature, bone fracture, compressive neuropathies, hypocalcemia-induced seizures, and life-threatening pancytopenia[1]. Sclerosis within the skull causes compression of the optic nerve and visual impairment in approximately 42% of patients[2,3]. Signs and sequelae manifest within the first months of life.

Diagnosis of IMO is based on clinical history, examination, and radiographic evidence of uniformly dense, sclerotic, and radiopaque bones with increased cortical thickness and decreased medullary canal diameter with a "bone-within-bone" appearance, especially in the vertebrae[3,4]. Biochemical elevations in tartrate-resistant acid phosphatase and creatinine kinase brain isoenzyme can support a diagnosis, while genetic testing is definitive[1,4]. If untreated, life expectancy is <5 years and related to bone marrow suppression[5]. The only curative treatment is an early allogeneic hematopoietic stem cell transplantation (HSCT) with myeloablative regimens that lead to engraftment of donor macrophage-derived osteoclasts, bone remodeling, and the establishment of normal hematopoiesis[6-8]. In a study by Driessen et al, the 5-year disease-free survival was 73% for recipients of a genotype HLA-identical HSCT, while only 40% for recipients of a matched unrelated donor[2].

Herein, we report a case of childhood osteopetrosis treated with an allogeneic HSCT who developed a secondary advanced, anaplastic lymphoma kinase (ALK)-mutated non-small cell lung cancer (NSCLC) (Figure 1A/B). The patient was started on alectinib, a highly selective inhibitor of ALK , and experienced an excellent radiographic response that is maintained a year later (Figure 1C).

Brief Report

A 28-year-old male presented with a four-month history of fatigue, malaise, and voice changes. His symptoms were suspected to be related to the COVID-19 virus, but testing was negative and diagnosed as pharyngitis

with supportive management. The following month, his symptoms persisted, and he developed anorexia, early satiety, weight loss, and migratory pain in the lower back and abdomen.

At age two, the patient received an allogeneic HSCT with busulfan and cyclophosphamide conditioning chemotherapy and total body irradiation (TBI) for osteopetrosis. Sequelae of his disease include bilateral vision loss and congenital cataracts. He remained on surveillance for twenty years at The Hospital for Sick Children and then his primary care physician. He lives independently, works fulltime, and does not use alcohol/tobacco.

At initial assessment, there was tenderness to palpation of the right upper abdominal quadrant without peritoneal signs or hepatosplenomegaly. Laboratory testing revealed microcytic anemia, CA 19-9 tumor marker of 1715, and negative HIV and hepatitis testing. CT imaging identified an irregular 9 mm nodule in the posteromedial left upper lobe of the lung with osteosclerotic, hepatic, and splenic metastases, and diffuse lymphadenopathy. A hepatic biopsy demonstrated TTF-1 and Napsin-A positive carcinoma consistent with metastatic pulmonary adenocarcinoma, PD-L1 expression >50% (Figure 2A), and an *ALK*translocation was identified by FISH (Figure 2B).

Discussion

The development of secondary malignancies (SM) after an allogeneic HSCT remains a serious complication with considerable morbidity and mortality and a cumulative incidence of 10-12% at 15 years. The main factors for developing SM after an allogeneic HSCT include genetic predisposition, cytotoxic conditioning chemotherapy, radiotherapy dose/field, the length and severity of immunosuppression post-transplantation, and infection with hepatitis or Epstein-Barr viruses[9-11]. Specifically, a single TBI dose of 600-1200 centigrays (cGy) or a fractionated dose totaling 1440-1750 cGy have increased risk[12]. The most common SM include post-transplant lymphoproliferative disease (PTLD), acute leukemia (AL), myelodysplastic syndrome (MDS), and secondary solid cancer (SSC). While the median time to development of PTLD and AL/MDS are <1 year and 1-2 years, respectively, the latency period of a SSC is prolonged with an increasing risk throughout the patient's life that does not plateau[9,13,14].

Patients who receive an allogeneic HSCT have a 2–36-fold increased risk of developing a SSC. Large retrospective series estimate the median time to development as 3.3–6.8 years from transplantation and the cumulative incidence is 10-15% by 15-years[9,14-17]. The risk of invasive SSCs is strongly related to both the patient age and exposure to radiation as part of the conditioning regimen[18]. Children that received a HSCT <10-years-old have a higher risk of SSC (relative risk [RR] of 3.8), which increases to 55-fold if they received TBI[9,12,18,19]. In a study that included patients who received a HSCT for childhood non-malignant hematological diseases, the median age of diagnosis of a SSC was 21-years-old, the overall RR was 3.8, and the incidence of SSCs was 3.5% at 10-years and 12.8% at 15-years[20].

Common sites of SSCs after an allogeneic HSCT include the skin, oral cavity, thyroid, brain, breast, and lung[11,14,18]. In a large 2018 European study, lung cancer was the most frequent site of a SSC followed by breast, colorectal, prostate, and melanoma[22]. Interestingly, in a large cohort study by Majhail et al examining patients that received busulfan-cyclophosphamide conditional chemotherapy before an allogeneic HSCT, NSCLC was the most common SSC, which is alike to our patient's case. In this study, the overall median time to SSC was 6 years and 4.5 years for lung cancer; however, our patient developed his SSC approximately 26 years after transplantation[21]. There is no mention if the patients in this study also had an *ALK* , or other, mutation.

ALK gene rearrangement is detected in 3–7% of NSCLCs and typically occurs in younger patients without a history of tobacco use and histology of adenocarcinoma. The use of *ALK* tyrosine kinase inhibitors (TKIs) and targeted therapy has revolutionized the management of *ALK* -mutated NSCLC and translated into improved RRs, quality of life, progression-free survival (PFS), and overall survival (OS)[23]. In the PROFILE 1014 trial, first-line therapy of first-generation crizotinib demonstrated a significantly longer median PFS (10.9 v 7 months) and median OS (mOS) (NR v 47.5 months) than chemotherapy and a higher probability of survival at 4-years[24]. Due to acquired resistance, subsequent generations of *ALK* -directed

therapy were designed with improved binding capacity to the echinoderm microtubule-associated protein-like 4 fusion protein and the ability for central nervous system (CNS) penetration, thus, superseded crizotinib in the first-line setting[23]. In the randomized phase III ASCEND-4 and ALEX trials, ceritinib and alectinib demonstrated superior PFS and delay in CNS progression compared to crizotinib[25,26]. Furthermore, in two phase II studies, alectinib showed not only activity against CNS metastases but also the ability to prevent CNS metastases[27].

There is very little data available regarding the optimal treatment strategies for SSCs after a childhood HSCT. Conventionally, SSCs are treated based on the approved standard of care guidelines for the respective primary cancer site[14]. In a single-center cohort study by Baker et al, the average mOS for patients with a SSC after a HSCT was 4.5 years and the 5-year OS was 44%[17]. Data from a large cohort study by Tichelli et al suggests that outcomes in patients with a SSC after a HSCT depends strongly on the type of cancer, and potentially better if an allogeneic vs. autologous HSCT. Each tumour site is classified into a favorable, intermediate, or poor outcome group. Within the poor outcome group, the patient's SCC was the cause of death, while on 50% in the favorable group[22]. In 2015, Inamoto et al established cancer screening guidelines for HSCT patients and all SSC sites[28]. Awareness of the incidence of SSCs after a HSCT and the appropriate screening are essential for an early diagnosis and the possibility of improved outcomes[29].

To our knowledge, this is the first case report of *ALK*translocation driven NSCLC successfully treated with a targeted therapy after a childhood allogeneic HSCT for osteopetrosis.

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Figure Legend List:

Figure 1A: Thoracic CT Scan Identifying a New Diagnosis of Left Lung NSCLC

Figure 1B: Abdominal CT Scan Identifying New Hepatic Metastases

Figure 1C: Abdominal CT Scan Demonstrating an Intrahepatic Therapeutic Response While on *ALK* Targeted Therapy

Figure 2A: PD-L1 IHC Expression from a Metastatic Liver Lesion Biopsy

Figure 2B: *ALK* IHC Expression from a Metastatic Liver Lesion Biopsy