Case Report

Leprosy Reactivation and Lepromatous Gangrene Associated with Chemotherapy for Advanced Gastric Cancer: A Case Report and Review of the Literature

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Abstract

Immunity suppression is frequent among cancer patients and is further exacerbated by antineoplastic chemotherapy. It is usually complicated by opportunistic viral, microbial or fungal infections and less frequently involves reactivation of chronic infections. Herein we present a rare case of leprosy reactivation in a patient with advanced gastric cancer who had received first-line chemotherapy. Lepromatous lesions reactivation was complicated with thrombotic angiopathy that led to lepromatous gangrene and subsequent amputation of the left hand. The pathophysiology of this rare entity is discussed and the potent role of immense immune reactions, including the anti-phospholipid syndrome and its subsequent thrombotic complications is also addressed.

Introduction

Immunity disorders including anosoparesis, hypogammaglobulinemia and immune evasion are paraneoplastic features that are associated with a wide variety of human malignancies. Immunosuppression as a result of antineoplastic chemotherapy is also frequently observed in cancer patients, rendering them susceptible to infectious complications. Chemotherapy-induced neutropenia and lymphopenia and impairment of cellular immunity further increase the risk for new opportunistic infections or reactivation of chronic ones. Herein, we present a case of leprosy reactivation that led to the rare complication of lepromatous gangrene and subsequent amputation in a male patient with adenocarcinoma of the stomach that was subjected to first line chemotherapy.

Case Presentation

A 76-year-old man was admitted in our hospital with fatigue of recent onset and microcytic anemia (Hct: 25%), while the rest of the laboratory tests were unremarkable. His medical history included lepromatous leprosy that was diagnosed at the age of 12 and was successfully treated with dapsone. He was a social drinker and smoker. The patient underwent upper gastrointestinal tract endoscopy that revealed an extensive ulcerative lesion at the major arch of the stomach. Pathological examination of the biopsies established the diagnosis of an infiltrative mucinous adenocarcinoma of
the stomach with signet-ring cell morphology. Imaging studies of the abdomen and thorax revealed peritoneal implantations and liver metastases. The patient received first line chemotherapy with six cycles of Docetaxel (75mg/m² on Day 1), Carboplatin (area under the curve 5, on Day 1) and Capecitabine (2000 mg/m² on Days 1 to 5) every three weeks. Primary prevention for neutropenia with filgrastim was administered from the first cycle. However, grade III neutropenia at the third cycle led to 10% decrease in docetaxel and carboplatin doses. Subsequent imaging studies showed partial remission of the disease according to the RECIST criteria and the patient was referred to the outpatient Oncology clinic for periodic follow-up. He experienced no other substantial toxicity during chemotherapy.

Two months after the completion of first line chemotherapy, the patient presented with reddish skin lesions in the interdigital area of his left hand (Figure 1) and his nose (Figure 2). Biopsy of the hand lesion was compatible with chronic granulomatous disease. Due to the patient’s medical history, a nasal smear was examined with Ziehl-Nielsen staining and was found positive for acid-fast bacilli (Figure 3). The combination of the clinical signs and the nasal smear findings suggested the diagnosis of leprosy relapse. The lesion in the left hand expanded rapidly and became necrotic (Figure 4) despite oral broad spectrum multi-drug treatment (MDT), including rifampicin, ciprofloxacin and doxycyclin.
Doppler sonography of the hand disclosed severe thrombotic angiopathy of the small branches of the left radial and ulnar arteries with critically reduced blood perfusion and the patient was referred to the plastic surgery department for amputation at the carpal level. After surgery, the patient continued antibiotic treatment for mycobacterium leprae infection and thalidomide, as an immunomodulator, was added to the regimen. One month after amputation the patient was free of symptoms, experiencing no signs or clinical evidence of active infection. Unfortunately, two months after amputation the patient experienced disease progression in the abdomen and despite second-line chemotherapy he died from metastatic disease in August 2011.

**Discussion**

Immunoevasion is an emerging hallmark of cancer cells [1]. Due to genomic instability (a hallmark of transforming cells [2]) and selective pressure from host immunity mechanisms [3], transforming cells adopt phenotypical characteristics that allow their unrestricted proliferation [1, 3]. These mechanisms include: the avoidance of cytotoxic lymphocyte stimulation by attenuation of human leukocyte antigen class (HLA) molecules and the suppression of tumor-infiltrating immune cells activity by
molecular and cellular factors [4]. In addition, cancer cells excrete immune suppressive factors (including vascular endothelial growth factor or VEGF, IL-10, and PGE2) that exert systemic effects on immune cell function [5, 6], thus, compromising the host’s native and adaptive immunity. Under this setting, immune suppression is clearly observed in cancer patients.

The function of the immune system in cancer patients is further impaired by the applied treatment modalities. Both radiotherapy and the majority of the chemotherapeutic agents inhibit proliferation and maturation of the myeloid lineage in the bone marrow resulting in increased risk for neutropenia and subsequent bacterial or fungal infections [7]. Moreover, certain chemotherapeutic agents cause lymphopenia [8] or affect lymphocytic function, directly inhibiting both humoral and cellular immunity [9]. Finally, corticosteroids that are frequently used during chemotherapy have similar adverse effects on T- and B-cell activation [10].

The integrity of cellular immunity is indispensable for the prevention of opportunistic infections, including pneumonocystis jiroveci pneumonia (PJP) or the reactivation of mycobacterial infections [11]. Malignant disease and chemotherapy have been long recognized as risk factors for the development of tuberculosis [12]. Despite the higher incidence of mycobacterium tuberculosis infections in patients with malignant lymphomas, certain solid tumours, such as lung, head and neck and stomach carcinomas have also been associated with the development of tuberculosis [13]. To the best of our knowledge, this is the first case of relapse of M. leprae infection in a cancer patient receiving chemotherapy reported in the literature. Diagnosis of leprosy is based mainly on the combination of its characteristic clinical signs and detection of acid-fast mycobacteria in liquid smears or skin biopsies of the patient. Paucity of data could be surely attributed to the “elimination” of the disease (reduction in prevalence in less than 1 per 10,000 population) in most parts of the world with the exception of endemic areas (e.g. India, Brazil). Furthermore, in the era of multi-drug therapy (MDT) of leprosy, patients receiving adequate treatment should be considered as “cured” since the incidence of relapse is below 1% within 9 years after MDT completion [14]. However, older patients that were treated with dapsone as monotherapy – alike our case – are declared as “disease arrested”
and they present 10 times greater risk for disease relapse than patients receiving MDT [14].

In the present case, the patient received a docetaxel-based combination as first line therapy for his non-operable gastric adenocarcinoma. Docetaxel is known to reduce the number of peripheral blood lymphocytes [8, 15-17] and also to suppress major histocompatibility-unrestricted cytotoxicity of T lymphocytes [16]. Furthermore, docetaxel inhibits Toll-like receptor 4 (TLR-4) signaling [18], that is implicated along with TLR-2 in the initiation of the immune response against mycobacteria [19, 20]. However, the significance of this mechanism in the role of docetaxel in inducing leprosy relapse should be further examined, since recent data correlate dysfunctional TLR-4 single nucleotide polymorphisms with protection against M. leprae [19].

Lepromatous gangrene is a rare complication of lepromatous leprosy that is usually attributed to thrombotic microangiopathy and involves mainly the extremities. However, recent evidence suggests an important role of the anti-phospholipid antibodies in the lepromatous gangrene pathophysiology [21]. Anti-phospholipid antibodies (APLA) have been originally described in the anti-phospholipid syndrome that can occur either in its primary form or secondarily in association with other autoimmune disorders or various infections, including syphilis, HIV, HCV disease, tuberculosis and cytomegalovirus infection. Of note, increased APLA levels were also reported in 29% among 112 leprosy patients in one study [22]. It is, thus, probable that infection-induced increased APLA are associated with the thrombotic manifestations of the anti-phospholipid syndrome that complicated leprosy re-activation in our case. However, anti-cardiolipin antibodies (ACLA), APLA and lupus anticoagulant were negative in our patient and tests for other hypercoagulable states (protein C, protein S, antithrombin III, homocystein and factor V Leiden) were within normal limits. Moreover, histopathologic findings of the lesion biopsy in our patient showed microvascular thrombosis in the absence of inflammatory infiltration of the vessel wall, a situation which is frequently described as the Lucio’s phenomenon [23]. Therefore, a clear etiopathological association between APLA and lepromatous gangrene could not be established in our case, as it was in a similar one recently reported in the literature [21]. Nevertheless, the beneficial
effect of thalidomide - an agent with well defined immunomodulatory properties in autoimmune disorders - in our patient suggests a potent role of immune reactions in thrombotic complications associated with leprosy re-activation [24, 25].

**Conclusion**

Leprosy reactivation is a rare complication of chemotherapy due to the low prevalence of the disease and the current use of multidrug therapy (MDT) for its treatment. The attenuation of cellular immunity though caused by the neoplasia itself and the commonly used chemotherapeutic agents increase the risk for mycobacterial and opportunistic infections in cancer patients. In this setting, new reddish patches with loss of sensation or thickened peripheral nerves should raise high clinical suspicion for leprosy relapse in a patient with previously treated Hansen’s disease. Moreover, thrombotic complications, including the rare entity of lepromatous gangrene should always be anticipated and treated aggressively in parallel with the infection. The potent role of overt immune reactions in thrombotic disease justifies the use of immunomodulatory agents, such as thalidomide, along with anticoagulants, for the treatment of this serious complication.

**References**


