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INJECTION SITE REACTION AND TUMOR LYSIS SYNDROME WITH BORTEZOMIB - A CAUSAL RELATIONSHIP OR A MERE COINCIDENCE

Oncology

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ABSTRACT

Bortezomib is a first line therapy in multiple myeloma and skin reactions are common with this drug. However, most of the reactions are generalized and are immune mediated. Less common reactions are seen at the injection site when administered subcutaneously which typically manifests as an erythematous patch. We present a case of 61 year old woman with severe multiple myeloma treated with s.c. bortezomib which lead to an atypical cogwheel injection site reaction. With the second dose, she developed a similar reaction but was milder. Interestingly she had a severe tumor lysis syndrome immediately following the first dose which corresponded with the severity of the skin reaction which was milder after the second dose. This rash was self-limiting and did not require any specific therapy. It remains unclear whether the severity of ISR correlates with tumor burden, as occurs with TLS or it is idiosyncratic. A clinician's familiarity with possible cutaneous manifestations of the cancer being treated is crucial as new drug reactions can occur with every dose and need to be differentiated from cancer itself.

KEYWORDS

Bortezomib, drug reaction, injection site, adverse effect, multiple myeloma, tumor lysis syndrome

INTRODUCTION

Bortezomib, a proteasome inhibitor, is being used as first-line therapy in multiple myeloma since the early 2000s (1). This drug has myeloma specific activity as it prevents NFκB translocation to the nucleus resulting in inactivation of multiple downstream pathways (2). It can be administered as a subcutaneous (S.C.) or intravenous (I.V.) injection on several days for up to 9 cycles in combination with other chemotherapy drugs. S.C. bortezomib has equal efficacy to I.V. preparation with an added advantage of better safety profile (3). Adverse skin reaction is a common occurrence with this route of administration. We report an atypical reaction secondary to S.C. Bortezomib in a patient with high-grade multiple myeloma.

Case Report

A 61-year-old woman who presented to the office with chronic low back pain for several weeks, with recent worsening over 2 weeks. She also noted right lower chest wall pain for 3 days. Examination was significant for tenderness over the inferolateral right 6th rib in the mid-axillary line. There was no midline spinal tenderness but a straight leg raise test was positive on the right side. Magnetic resonance imaging of the lumbar spine revealed diffuse abnormal marrow signal conversion in the T2 signal from fat to cell. This prompted further blood investigations, which revealed hemoglobin of 10 g/dL, normal serum iron levels (46 ug/dL), total protein 11.2 g/dL, uric acid 11 mg/dL, and LDH of 1147 U/L. Serum electrophoresis showed elevated IgG lambda paraprotein of 6.4 g/dL and beta 2 microglobulin level of 5899 ng/mL. Bone marrow biopsy showed infiltration with greater than 90% plasma cells. Genetic testing revealed a high-risk plasma cell clone with 1q duplication, IGH/MAF fusion, representing a t(14;16), trisomies 3 and 7, and monosomy 13 (4). Computed tomography of the chest and abdomen showed multiple osseous lesions involving vertebrae and ribs. High-grade multiple myeloma was diagnosed and she was started on chemotherapy with bortezomib, lenalidomide, and dexamethasone. Bortezomib was dosed on days 1, 8, and 11 along with lenalidomide 25 mg from days 1 through 14 and dexamethasone on 1,8 and 15 days. Bortezomib was administered subcutaneously in the abdominal wall at a dose of 1.3 mg/m2. one day later, patient-reported a 3 x 3 cm sized well-demarcated patch with erythematous center at the injection site (Figure 1A). Shortly thereafter, she developed severe tumor lysis syndrome (TLS) with LDH of 8950 U/L, phosphorus 5.7 mg/dL, calcium 6.2 g/dL, blood urea nitrogen (BUN) 51 mg/dL, AST 834 U/L and ALT 77 U/L. She was treated with aggressive fluid resuscitation. By day 4 her LDH was down to 3717 U/L. On day 4, the skin lesion was noted to have a cogwheel appearance with central sparing (Figure 1B). The second dose of Bortezomib was delayed and was given on day 10 after TLS resolved. Due to prior abdominal skin reactions, the second dose was administered in the thigh at the same dose. On Day 1, mild erythema was observed (Figure 2A). By day 4, the lesion evolved to a milder form of a reaction similar to the one seen with the first injection with associated desquamation (Figure 2B). TLS was less severe with the second injection (LDH 1489 U/L, BUN 23 mg/dl, AST 130 U/L, calcium 7.6 g/dL).

DISCUSSION

Chemotherapeutic agents can cause a variety of dermatologic changes. Protean in presentation, these changes may be related to cancer itself or develop as an adverse drug reaction. A clinician's familiarity with possible cutaneous manifestations of the cancer being treated is crucial as new drug reactions can occur with every dose and need to be differentiated from cancer itself. Bortezomib can cause a variety of erythematous skin reactions including papular rash, plaques, or nodules (5). Skin reactions can occur in up to 19% of patients receiving this chemotherapy agent (6). The majority of these are secondary to cutaneous vasculitis and tend to occur at a site different from the injection site, commonly following the 3rd or 4th dose. Skin biopsy is typically not performed. In mild cases, topical steroids are recommended. Vasculitic rash is considered as a surrogate marker for the clinical response (6). In severe cases, a pulse dose of steroids along with antihistamines are used. Pre-treatment with steroids help in such scenarios (5). On the contrary, injection site reactions (ISR) are much less common than generalized reactions. Incidence with S.C. injection is approximately 6% and the majority are mild hyperpigmentation reactions which usually resolve in 6 days. The mechanism is irritant cytotoxic injury due to extravasation into the adipose. Several techniques are employed to decrease these reactions including proper skin fold technique, angle of injection, and appropriate needle size (7). Abdomen and thigh are the two most common sites utilized. There is very limited research on ISRs secondary to Bortezomib. A Japanese study reported that abdominal injections caused fewer reactions compared to the thigh, and the reactions are more likely to occur with the first dose than the subsequent cycles (8). Interestingly, our patient had a severe reaction in the abdominal site compared to the thigh and this could be related to the first administration to the abdomen. The most common reaction is erythema or hyperpigmentation at the site.

Rarely atypical reactions occur and can include induration and scab formation (7). Obeid KM et al reported a small boil-like lesion which subsequently became extensive requiring methylprednisone (9). Premedication with steroids would not reduce the ISR as seen in our case. A cogwheel pattern of skin reaction has never been reported. It is important to identify these skin reactions so as to change the site with each injection and to take proper precautions along with good injection techniques. Skin biopsy is not always warranted unless the reaction is severe. However, in our patient, we noticed that with the first dose, there was severe TLS as well as severe ISR, both of which were less significant with the second dose. It remains unclear whether the severity of ISR correlates with tumor burden, as occurs with TLS or it is idiosyncratic. ISR in most cases is mild, self-limiting, and in our patient it started resolving by day 4.

Figures

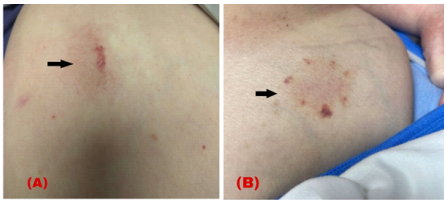

Figure 1: Skin changes after first dose of Bortezomib A) 3 x 3 cm sized well-demarcated patch with erythematous center at the injection site (day 1); B) cog-wheel pattern with central sparing (day 4)

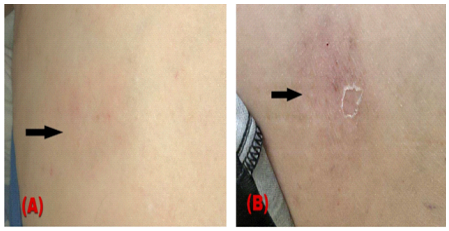

Figure 2 : Skin changes after second dose of Bortezomib A) mild erythematous patch without clear demarcation (day 1) B) milder cog-wheel pattern with desquamation (day 4)

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