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Injection-Site Reaction Following 5-Azacitidine Injection

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Dear Editor:

Azacitidine (Vidaza) is a pyrimidine nucleoside analogue of cytidine, which is injected subcutaneously to treat patients with myelodysplastic syndrome (MDS). Among azacitidine recipients, injection-site reactions are one of the most common non-hematological adverse events[1]. A 76-year-old man with MDS was treated with subcutaneous 5-azacitidine, which was injected into the left lower abdomen. The patient complained of severe pain, and an ecchymotic patch with bulla was visible at the injection-site (Fig. 1) at day 7, even though this therapy had been well tolerated during the initial 6 days of treatment. Histological examination revealed intraepidermal vesicles and massive hemorrhage in the upper dermis, with dense perivascular lymphohistiocytic infiltration in the dermis and subcutis. Two weeks later, the lesion had converted into a necrotic crust, which subsequently healed 1 month later, leaving an atrophic scar. Subsequently, the patient had been treated with 5-azacitidine for 3 months without any adverse events, although 5-azacitidine treatment for MDS was stopped due to a lack of clinical response. Clinicians should consider whether an injection site ecchymotic erythematous patch, with bulla is an injection-site reaction and/or Nicolau syndrome (NS). Azacitidine is a hypomethylating agent that is subcutaneously injected to treat patients with MDS. Administration-related skin events are typically erythema and injection-site reactions, such as skin nodules, rash, and pyoderma gangrenosum[2]. Azacitidine has a cytotoxic effect on all cells (including abnormal hematopoietic cells), and when injected subcutaneously, it can cause direct damage to the skin cells, such as keratinocytes and endothelial cells, subsequently leading to skin necrosis. NS is also characterized by intense pain and erythematous-ecchymotic lesions at the injection-site, and can lead to necrosis of the skin. Various drugs have been reported to be associated with NS, including diclofenac, antibiotics, vitamin K, glucocorticoids, lidocaine, anticonvulsants, and vaccines. However, NS has also been reported following subcutaneous injection of, glatiramer acetate and etanercept[3]. The pathogenesis of NS is not well understood, although there have been two hypotheses. Firstly, intra-arterial or perinervous injections might stimulate the sympathetic nerve, causing an acute vasospasm of the vessel, leading to ischemia. Secondly, periarterial or intra-arterial injections might cause direct trauma to, or inflammation of, the vessel structures, followed by thrombosis and necrosis[4]. Therefore, histological findings indicative of NS are typically associated with thrombosis and/or necrosis of the eccrine sweat glands. In this case, we could not find

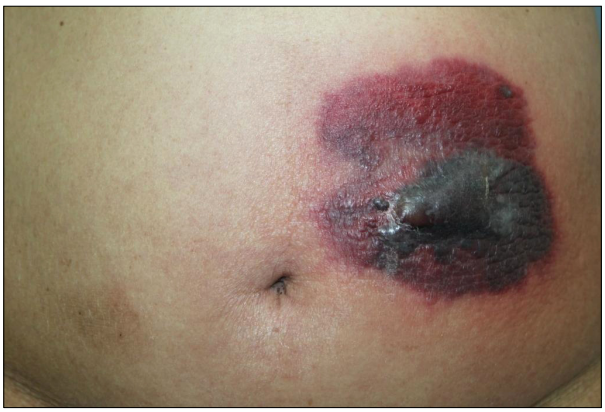

Fig. 1. An ecchymotic erythematous patch with bulla is visible on the abdomen where the 5-azacitidine was injected.

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any histopathological evidence of thrombosis, and thus the diagnosis of injection-site reaction of 5-azacitidine was made based on a combination of clinical and histopathological findings. Most injection-site erythema/reactions are resolved by simple continuing treatment, and less than 12% of cases require corticosteroids and/or antihistamine[2]. A correct injection technique, such as syringe aspiration, and injection-site rotation, can help prevent injection-site reaction.

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Upregulated Expression of Calcyclin-Binding Protein/Siah-1 Interacting Protein in Malignant Melanoma

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Dear Editor:

The calcyclin-binding protein (CacyBP) was initially named for its ability to interact with calcyclin (S100A6) at a physiological range of Ca^{2+} concentration[1]. However, Matsuzawa and Reed[2] found that the human analog of mouse CacyBP interacted with Siah-1 and named this protein the Siah-1 interacting protein (SIP); therefore, it is now widely called CacyBP/SIP. Additionally, CacyBP/SIP and Siah-1 associate with Skp-1, acting as an ubiquitinating complex that degrades non-phosphorylated β-catenin in the presence of p53[2].

In breast cancer, CacyBP/SIP mRNA and protein levels were significantly higher than that of adjacent non-tumor tissues. Poor cellular differentiation, lymph node invasion,

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