



## Work up for the clopidogrel hypersensitivity that led to recognising the undiagnosed myelodysplastic syndrome

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Antiplatelet therapy with clopidogrel is widely used as a preventive strategy in patients with acute coronary syndrome, particularly after stent implantation.<sup>[1]</sup> Diverse manifestations of clopidogrel hypersensitivity reaction have been reported including cutaneous,<sup>[1,2]</sup> and hematologic symptoms<sup>[3]</sup> as well as fatal reactions including thrombotic thrombocytopenic purpura (TTP).<sup>[4]</sup> Clopidogrel cutaneous hypersensitivity reaction has been reported to occur on day 6 ± 2 of therapy.<sup>[5]</sup> However, Shetty, *et al.*<sup>[6]</sup> recently reported a case of leukocytoclastic vasculitis that appeared after one year of clopidogrel therapy. Here, we report the case of a patient with clopidogrel hypersensitivity that led to recognising the undiagnosed myelodysplastic syndrome (MDS).

A 78-year-old female visited the emergency department on October 2013 with severely itching confluent purpuric patches with vesiculation and wheal-like erythematous patches on the trunk and extremities that appeared one day prior (Figure 1). She had been taking clopidogrel since September 2011, which was started after percutaneous coronary intervention. Concomitant drugs included simvastatin, isosorbide, and sitagliptin. The patient presented with a fever (38.5°C). Laboratory tests revealed anemia (11.2 g/dL), leukocytosis (12,000/μL) with neutrophilia, and marked thrombocytopenia (25,000/μL) with normal liver and renal function. Neither eosinophilia nor lymphadenopathy was observed. TTP was ruled out by the absence of schistocytes and a normal von Willebrand Factor (vWF) multimeric pattern. Systemic and topical steroids as well as antihistamines were prescribed with simultaneous discontinuation of all drugs except sitagliptin under suspicion of drug hypersensitivity reaction. After three days, symptoms were alleviated and the patient restarted simvastatin and isosorbide, as these medications were unlikely to have caused drug hypersensitivity. Skin biopsy revealed superficial perivascular lym-

phocyte and eosinophil infiltration, and leukocytoclastic vasculitis which were consistent with drug hypersensitivity reaction.

We referred her to a hematologist to manage hematologic abnormalities and to evaluate possible sources of thrombocytopenia other than clopidogrel hypersensitivity, since her lab findings had worsened after initial treatment. The patient had been aware of her anemia and low-normal-range platelet counts for several years, for which she did not seek further evaluation. After thorough hematologic lab tests, bone marrow biopsy, and genetic analysis (46,XX,del(20)(q11.2)[15]/46,XX[5]), refractory cytopenia with multilineage dysplasia, a subtype of MDS, was diagnosed.

Two weeks of treatment with steroid and antihistamine markedly improved skin lesions and itching. The hematologist restarted clopidogrel in December 2013. About a month later, she revisited the dermatology clinic with similar, but milder symptoms, which were successfully managed with systemic and topical steroids. Based on her clinical symptoms, histopathological findings, and recurrence after re-exposure to clopidogrel, late-onset clopidogrel hypersensitivity was diagnosed.

As for management of MDS, the hematologist started supportive care with red blood cell and platelet transfusion. Due to advanced age, the patient was not considered eligible for allogeneic hematopoietic stem cell transplantation (HSCT). Alternative treatment with acacitidine was started in April 2014. Unfortunately, the patient died due to pneumonia as complication of chemotherapy.

Clopidogrel hypersensitivity usually occurs within a week of drug commencement and manifests as various cutaneous symptoms and hematologic abnormalities.<sup>[1,5]</sup> The most common cutaneous lesion seen is generalized exanthema, but urticaria, angioedema, and localized skin reactions such as desquamation and hyperkeratosis have been also reported.<sup>[1]</sup> Substitution with ticlopidine, clopidogrel desensitization or administration of systemic steroids with

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**Figure 1.** Confluent purpuric patches with vesiculation and wheal-like erythematous patches on the trunk and extremities. (A): anterior trunk; (B): posterior limb.

or without cessation of clopidogrel have been used to manage clopidogrel hypersensitivity.<sup>[1,5-7]</sup> Frequent laboratory tests and close observation are needed, because clopidogrel hypersensitivity can sometimes be fatal if not managed appropriately.<sup>[8]</sup>

The current case is unique in that the hypersensitivity reaction occurred over two years after initiation of clopidogrel and that the patient was subsequently diagnosed with MDS. Since non-specific skin lesions such as neutrophilic dermatosis, leucocytoclastic vasculitis, and Behçet disease are associated with MDS,<sup>[9]</sup> it is possible that MDS contributed to the development of the current cutaneous symptoms.

In order to diagnose clopidogrel hypersensitivity, it is important to recognize its diverse manifestations and the possibility of late-onset reaction. Further laboratory workup is also crucial for evaluating the possibility of hematologic diseases such as MDS when encountering clopidogrel hypersensitivity.

To our knowledge, there is only one published case of MDS associated with clopidogrel.<sup>[10]</sup> Interestingly, MDS was also diagnosed about 3 years after clopidogrel treatment just like the present case. However, there was no cutaneous clopidogrel hypersensitivity in the previous report. MDS associated with medication or therapy-related MDS (t-MDS) is usually induced by alkylating drugs, topoisomerase II inhibitor, and ionizing radiation with a latent period of 2–8 years.<sup>[11]</sup> Risk of t-MDS has been related to total dose, duration, and specific type of alkylating agent.<sup>[12]</sup> As for MDS associated with clopidogrel, there is little evidence to suggest it is dose-dependent.<sup>[10]</sup>

Three medications (azacitidine, decitabine, lenalidomide) are currently approved by the US Food and Drug Administration for MDS. These agents can improve hematopoiesis, delay disease progression, and improve quality of life in certain patients.<sup>[11]</sup> Especially, azacitidine has been shown to

improve overall survival in higher-risk MDS patients compared to supportive care.<sup>[13]</sup> Unfortunately, these medications will fail in the majority of patients within 2 to 3 years after treatment initiation even after initial favorable response.<sup>[11,14]</sup> The only potentially curative therapy for MDS is allogeneic HSCT.<sup>[14]</sup> However, less than 10% of MDS patients undergo HSCT due to advanced age and serious comorbidities of the patient, and it is successful in only 20% to 50% patients.<sup>[11]</sup> Although there are limited clinical trials for t-MDS, it also can be treated with above-mentioned therapy.<sup>[15]</sup>

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