

# Clopidogrel-Associated Acute Generalized Exanthematous Pustulosis

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*Acute generalized exanthematous pustulosis (AGEP) is a skin eruption of rapid onset and progression that is characterized by the formation of numerous sterile pustules on an erythematous background. Other features may include fever and leukocytosis, with resolution usually in less than 15 days. We present an 83-year-old woman with an erythematous pustular eruption following placement of a bare metal coronary stent and initiation of anticoagulation with clopidogrel. She was diagnosed with AGEP after a biopsy was performed and other possible causes of a pustular eruption were excluded. Two medications—carvedilol and rosuvastatin—were initially viewed as possible culprits and were temporarily discontinued. However, the patient's rash continued to worsen. Additionally, she had a persistent low-grade fever, leukocytosis, and a slow rise in her creatinine level. Clopidogrel was discontinued and replaced with ticlopidine on day 7 of hospitalization. Within 48 hours her temperature, white blood cell count, and creatinine level began to improve. Her skin subsequently desquamated and she was sent home on day 20. We discuss drug-induced AGEP and a desensitization protocol that has allowed patients to resume use of clopidogrel following a prior cutaneous reaction to this medication.*

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leukocytosis, with resolution usually in less than 15 days.<sup>1</sup> More than 90% of cases have been found to be drug induced with antibiotics being the most common culprit.<sup>2</sup> We present a case of AGEP following administration of clopidogrel. Recognition of this reaction pattern is important given the frequent reliance on clopidogrel in preventing coronary artery restenosis after stenting.

## Case Report

An 83-year-old woman was admitted to the hospital with shortness of breath and an accompanying low-grade fever. Recent medical history included a myocardial infarction 1 week prior that required coronary stenting and initiation of anticoagulation with clopidogrel. An initial chest radiograph and computed tomography showed right upper lobe consolidation. Early sputum and blood cultures were negative. Because of a history of a positive tuberculin test in the patient and 2 other family members, she was placed in isolation and subsequently treated with intravenous levofloxacin as well as piperacillin and tazobactam for a presumptive diagnosis of bacterial pneumonia.

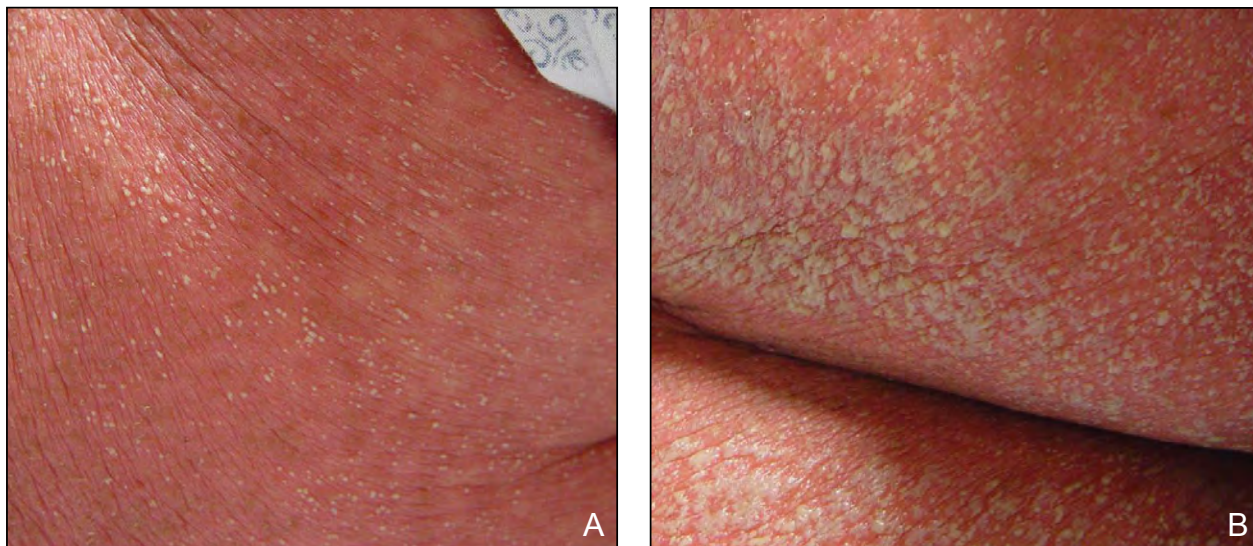
At the time of admission, she also presented with a predominantly truncal erythematous rash with a few overlying small pustules. The rash started just prior to release from the hospital after stent placement a few days earlier. A working diagnosis of a drug eruption was made based on examination. New medications in the last few months included clopidogrel, carvedilol, and rosuvastatin, which were viewed as possible culprits responsible for the rash. Carvedilol and rosuvastatin were both discontinued in the hopes that the rash would improve. Although clopidogrel most likely was the medication responsible for the rash from a chronologic standpoint, it was continued, as the patient was deemed to be at high risk for restenosis of her recently placed bare metal stent if clopidogrel was discontinued.

Three days later the low-grade fever persisted despite clinical and radiologic improvement in her pulmonary status. Additionally, she developed

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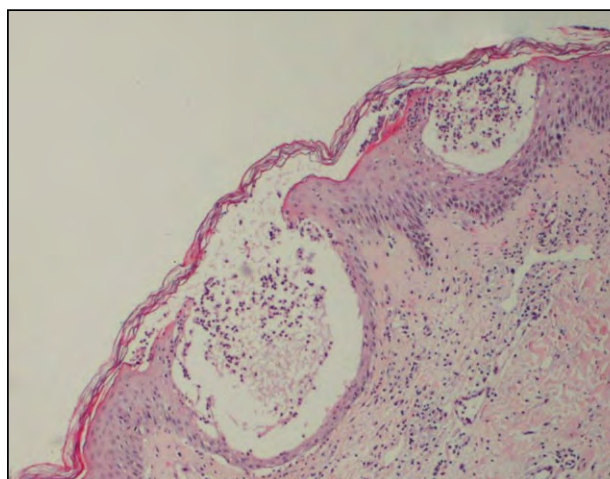
**Figure 1.** Numerous small pustules overlying diffuse erythema on the back (A). The pustules became confluent over the lower back (B).

leukocytosis and a slow rise in her creatinine level. The rash quickly progressed with the development of generalized erythroderma characterized by tiny pustules (Figure 1). A punch biopsy was performed and revealed subcorneal collections of neutrophils (Figure 2). Gomori methenamine-silver staining was negative. Bacterial culture of the skin also was negative. A diagnosis of AGEF was given with the recommendation that clopidogrel be switched to another medication if possible.

The eruption continued to worsen, and on day 7 of her hospitalization, the cardiology department obliged and switched clopidogrel to ticlopidine. Within 48 hours her temperature, white blood cell count, and creatinine level began to improve (Figure 3). This trend continued for the remainder of the hospitalization. Her skin subsequently desquamated and she was sent home on day 20 with ticlopidine in place of clopidogrel.

### Comment

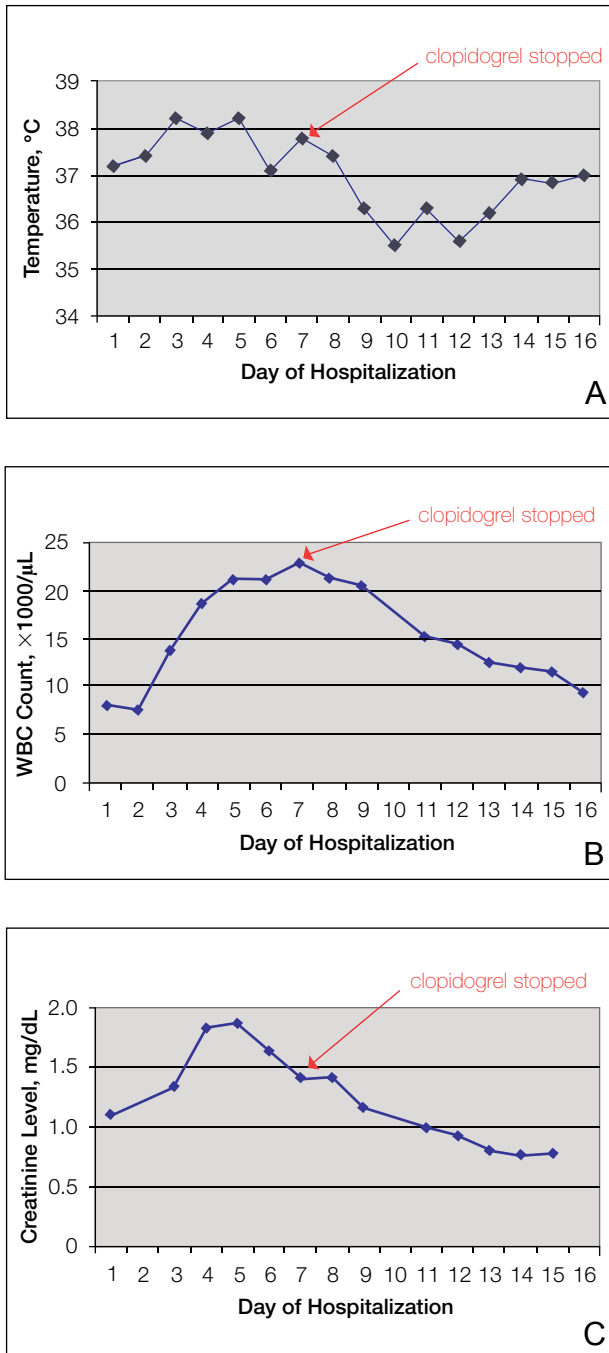
Acute generalized exanthematous pustulosis was first described in 1980 by Beylot et al<sup>3</sup> as an acute pustular reaction pattern distinct from pustular psoriasis. Characteristic features include numerous nonfollicular, subcorneal, sterile pustules overlying widespread erythema, fever (>38°C), and neutrophilic leukocytosis.<sup>4</sup> Symptoms resolve following discontinuation of the offending agent. The pustules last an average of 9 days and are followed by generalized desquamation of the skin.<sup>5</sup> Accompanying symptoms may include mild eosinophilia, hypocalcemia, and elevated liver function tests. Reversible renal failure is fairly common, occurring in one-third of reported cases.<sup>6</sup>



**Figure 2.** Punch biopsy of lesional skin showed subcorneal pustules (H&E, original magnification  $\times 10$ ).

The vast majority of cases are caused by drugs (>90%). Antibiotics are most commonly implicated, including  $\beta$ -lactams and macrolides. There also is a strong association with terbinafine, diltiazem, and hydroxychloroquine.<sup>7</sup> New medications are steadily being reported as triggers for AGEF as awareness of this cutaneous drug reaction increases. A small percentage of cases have additionally been found to occur secondary to acute viral infections, hypersensitivity to mercury, and spider bites.<sup>4,8,9</sup>

Skin findings occur shortly after exposure to offending medications. The median duration of time from drug exposure to onset of AGEF has 2 different



**Figure 3.** Recorded maximum body temperature (A), white blood cell (WBC) count (reference range, 4500–11,000/ $\mu$ L)(B), and creatinine level (reference range, 0.6–1.2 mg/dL)(C) during hospitalization. Clopidogrel was stopped on day 7.

patterns. With antibiotics, the reaction is seen rapidly, typically within 1 day; in contrast, with most other implicated drugs a reaction is experienced 11 days after initiation, which may reflect primary sensitization.<sup>7</sup>

Clopidogrel is a selective irreversible inhibitor of adenosine diphosphate–induced platelet aggregation. The drug is a thiopyridine that has been shown to be essential in reducing the risk for stent thrombosis after coronary artery stenting.<sup>10</sup> Although clopidogrel is well-tolerated by most patients, occasional adverse reactions occur. Reported cutaneous reactions have ranged from mild urticaria to a severe systemic hypersensitivity syndrome including fever and pancytopenia.<sup>11</sup>

When patients have a documented adverse reaction to clopidogrel, alternative options are limited. Ticlopidine, a related thiopyridine, exists as an alternative. However, cross-reactivity has been documented between these 2 closely related medications. Additionally, ticlopidine has a potentially serious side-effect profile, including diarrhea, thrombocytopenia, anemia, and neutropenia.<sup>12</sup> Use of alternative anticoagulants is deemed insufficient to prevent the risk for acute restenosis of bare metal and drug-eluting stents. Standard of care requires the use of clopidogrel for 6 weeks following placement of bare metal stents and for 6 months for drug-eluting stents. Patients who cannot tolerate clopidogrel or ticlopidine after stenting are at an increased risk for restenosis. Invasive and surgical procedures are tenuous in patients treated with clopidogrel.

Given the potential serious nature of AGEP in response to clopidogrel, it would not be prudent to rechallenge the patient with this medication. However, an oral desensitization protocol has been developed that may allow continuation of clopidogrel. According to a PubMed search of articles indexed for MEDLINE using the term *clopidogrel desensitization*, 11 reports have been published.<sup>12–22</sup> All patients developed pruritus and a rash within 1 to 3 weeks of starting the medication. The protocol involved administering the drug at half-hour intervals, starting at a very low dose and increasing up to a therapeutic level over the course of 8 hours. The patients were closely monitored in either an outpatient or intensive care unit setting for symptoms of hypersensitivity during this dose escalation. If a rash occurred, antihistamines and corticosteroids were given and the next doubling dose was delayed. Individuals undergoing the procedure as an inpatient remained in the hospital overnight for monitoring. No patients developed anaphylaxis with this procedure and all were able to resume use of clopidogrel.<sup>12–22</sup>

These results are promising; however, drug desensitization is thought to be most useful for IgE types of allergic reactions (type I hypersensitivity). Desensitization is believed to work by causing mast cells to become unresponsive to the medication, which

occurs by slow binding of IgE receptors with escalating drug doses without triggering the mast cells to release their contents.<sup>23</sup>

Although the precise immunologic mechanism behind AGEF has not been elucidated, it appears to be a T-cell process, evidenced by positive patch tests and lymphocyte transformation tests.<sup>24</sup> Both drug-specific CD4 and CD8 reactions occur, leading to the production of IL-5 and IL-8. It has been suggested that AGEF represents a type of delayed hypersensitivity reaction with predominantly neutrophils being activated,<sup>25</sup> which may limit the usefulness of drug desensitization in cases of AGEF, though it has never been tested. Regardless, clopidogrel desensitization appears to show promise for type I hypersensitivity reactions.

### Conclusion

Acute generalized exanthematous pustulosis is a rare and potentially serious adverse cutaneous reaction that occurs in response to many medications. Based on our case report, clopidogrel can now be added to the list of potential triggers. Because this medication has become a staple in the management of cardiac patients, medication reactions to clopidogrel will likely become more frequent. The clinician must be aware of the limited anticoagulation options for these patients as well as drug desensitization protocols that exist for clopidogrel, though these protocols are designed to allow continuation of the medicine following immediate hypersensitivity reactions as compared to exfoliative reactions seen with AGEF.

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