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Case Report

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A Case Report of the Eradication of *Pseudomonas aeruginosa* From Leg Ulcer in a Patient With Essential Thrombocythemia

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A patient treated with hydroxyurea had a lower extremity ulcer that was found infected with *Pseudomonas aeruginosa*. Drug discontinuation and ceftazidime treatment did not initially lead to resolution due to misidentification of inducible betalactamases expressed by the organism and subsequent clinical failure of the cephalosporin in eradicating infection. These class C enzymes may be strongly induced after betalactam exposure and confer resistance

to penicillins, cephalosporins, betalactamase inhibitors but not to carbapenems. Though hydroxyurea represents a major cause of essential thrombocythemia-related ulcers, lesion infections by difficult-to-treat organisms should be eradicated to promote wound healing.

Keywords: *Pseudomonas aeruginosa*; essential thrombocythemia; hydroxyurea; inducible betalactamases

Hematological causes of leg ulcers include polycythemia vera, sickle cell anemia, and essential thrombocythemia. Skin lesions represent one of the criteria on which diagnosis of resistance/intolerance to hydroxyurea (HU) in thrombocythemia patients is based. HU is a chemotherapeutic cytostatic agent that inhibits DNA synthesis during cell replication, thus causing death of phase S cells. The drug is used as a treatment for psoriasis, sickle cell disease, and myeloproliferative disorders. Skin ulcerations are a relatively uncommon adverse effect of long-term HU administration, the pathogenesis of which remains unclear.¹⁻⁴

Pseudomonas aeruginosa has been known to be one of the major causes of lower extremity wounds infections. Multidrug resistance by this species is common but frequently misdiagnosed, as clinical isolates are not always screened for the expression of inducible betalactamases. This makes it extremely

difficult to eradicate infecting strains from ulcers.⁵ We report the case of a patient with a myeloproliferative disorder and an infected ulcer.

A 50-year-old male patient with essential thrombocythemia developed a painful HU-related ulcer over his left lateral malleolus. The patient had been receiving HU for 15 months when the lesion developed. The wound had green exudate and was malodorous, typical of *P. aeruginosa*. Swabs were taken for cultures. Pending the outcome of microbiology results, intramuscular ceftazidime was initiated empirically. *P. aeruginosa* strain was cultured under aerobic conditions, wherein neither anaerobic nor microaerophilic organisms were grown. The isolate showed susceptibility to piperacillin (minimum inhibitory concentration [MIC] ≤ 4 $\mu\text{g/mL}$), piperacillin-tazobactam (MIC ≤ 4 $\mu\text{g/mL}$), ceftazidime (MIC 4 $\mu\text{g/mL}$), imipenem (MIC 4 $\mu\text{g/mL}$), meropenem (MIC 1 $\mu\text{g/mL}$), amikacin (MIC ≤ 2 $\mu\text{g/mL}$), and ciprofloxacin (MIC 1 $\mu\text{g/mL}$), whereas no in vitro activity was exerted by amoxicillin-clavulanate (MIC ≥ 32 $\mu\text{g/mL}$), cefoxitin (MIC ≥ 32 $\mu\text{g/mL}$), and cefotaxime (MIC ≥ 32 $\mu\text{g/mL}$), as expected. Strain identification was provided by the Vitek2 automatic system (bioMérieux, Marcy l'Etoile, France), whereas susceptibilities were obtained by Vitek2

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and confirmed by a CLSI (former NCCLS) disk method (disks by Liofilchem, Roseto degli Abruzzi, Italy).⁶

At this time the patient was receiving busulfan, due to ulcer development during HU therapy. Also, 2 weeks of ceftazidime treatment did not eradicate the infection, despite the apparent in vitro activity of the cited cephalosporin. We were unable to explain why ceftazidime was inactive in vivo against a fully in vitro susceptible organism, and we decided to perform a disk approximation test⁷ to screen the isolate for the expression of inducible betalactamases. These enzymes have recently gained significant clinical importance as they promote resistance to penicillins, cephalosporins, and aztreonam. Furthermore, these betalactamases are not affected by clavulanate, tazobactam, and sulbactam and leave a few therapeutic alternatives among betalactams (carbapenems). The prevalence of such enzymes has seen a significant rise in recent years, making their expression a serious clinical concern. Inducible betalactamases are known to belong to the class C AmpC hydrolase group and may be chromosome encoded or plasmid mediated.⁸⁻¹⁰ Unfortunately, they often remain undetected when only automatic and/or standard CLSI methods for susceptibility testing are performed, as repression of AmpC genes may result in lack of phenotypic resistance, unless gene expression is induced by exposure to betalactams. All these may act as inducers, but only carbapenems are never affected by AmpCs, though behaving as strong inducers, which is the reason why carbapenems (among betalactams) should be used in vivo as treatment against inducible hydrolase-producing organisms. This is also the reason why the disk approximation test is performed by placing cephalosporins, penicillins, and penicillin/betalactamase inhibitor disks close to imipenem and meropenem disks. We used a distance of 20 mm, from center to center; blunting of the betalactam inhibition zones on the induced size (towards carbapenems) is known to allow the labeling of clinical isolates as inducible AmpC producers. In the case reported, a clear cut of cefepime, ceftazidime, piperacillin, and piperacillin/tazobactam inhibition zones toward both the carbapenem disks was found on the agar surface; thus, the isolate was finally labeled as an inducible AmpC carrier. Clinical failure of ceftazidime was therefore explained by the fact that the cephalosporin acted as a betalactamase inducer, so that induced betalactamases affected ceftazidime itself, resulting in the

persistence of the infection. The cephalosporin was finally replaced by intramuscular imipenem, which led to infection resolution and gradual healing of the ulcer. This was because, though behaving as strong betalactamase inducers, carbapenems are not affected by AmpCs, thus retaining their in vivo bactericidal activity against AmpC producers.

Though the importance of inducible AmpCs in clinical practice is increasing, their role in causing ulcer treatment failure is still underestimated, partly because few clinical laboratories currently screen Gram-negatives for such enzymes; also, automatic systems for antibiotic susceptibility testing and standard disk methods may fail in detecting inducible mechanisms of resistance.¹¹ Our brief report focuses on misidentification of *P. aeruginosa*-inducible AmpCs as a cause for the persistence of infected HU-related ulcer, even after drug discontinuation.

A careful evaluation of this organism's susceptibility to betalactams other than carbapenems is always needed before starting therapy, or when in vitro susceptibility is documented but in vivo failure is observed. In particular, we would suggest clinicians and surgeons to routinely seek inducible AmpC screening in clinical laboratories, especially whether apparent cephalosporin susceptibility by *P. aeruginosa* isolates is documented, in order to obtain correct susceptibility data and reliable information about drug resistance epidemiology. We suggest that this is required to prevent clinical failure.

To conclude, treatment of HU-associated ulcers is difficult and usually requires prompt cessation of the drug.¹²⁻¹⁸ The role of infection in causing HU-related ulcer persistence and/or worsening should not be underestimated. Also, a careful evaluation of bacterial susceptibility profiles is needed to avoid antibiotic failure in ulcers treatment."

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