Pemphigus Vulgaris Aggravated: Rifampicin Found at the Scene of the Crime

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PRACTICE **POINTS**

- Long-term use of immunosuppressants requires constant attention for infections, especially latent infections in the body.
- Clinicians should carefully inquire with patients about concomitant diseases and medications used, and be vigilant about drug interactions.

Pemphigus vulgaris (PV) is a rare life-threatening condition of the pemphigus group of autoimmune blistering diseases. Systemic glucocorticoids are the cornerstone of management for PV, but complications can arise from their long-term use. We report a case of recurrence of a well-controlled case of PV that could not be alleviated by a combination of steroids, mycophenolate mofetil, and high-dose intravenous immune proteins. The patient had developed numerous complications during previous glucocorticoid therapy, including hypertension, diabetes, glaucoma, cataracts, optic nerve atrophy, aseptic necrosis of the femoral head, osteoporosis, and pulmonary tuberculosis. We determined that recurrence of PV and treatment resistance were consequences of the interaction between the antitubercular agent rifampicin that the patient was taking and corticosteroids. Pemphigus vulgaris was quickly controlled after the rifampicin was discontinued.

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Case Report

A 60-year-old man presented with eroded areas in the mouth and blistering eruptions on the scalp, face, trunk, arms, and legs. He initially presented to an outside hospital 4 years prior and was treated with oral prednisone 50 mg daily, to which the eruptions responded rapidly; however, following a nearly 5-mg reduction of the dose per week by the patient and irregular oral administration, he experienced several episodes of recurrence, but he could not remember the exact dosage of prednisone he had taken during that period. Subsequently, he was admitted to our hospital because of large areas of erythema and erosions on the scalp, trunk, arms, and legs.

Since starting the prednisone regimen 4 years prior, the patient had experienced onset of hypertension, diabetes, glaucoma, cataracts, optic nerve atrophy, aseptic necrosis of the femoral head, and osteoporosis. Biopsy of a new skin lesion revealed suprabasal acantholysis (Figure 1). Direct immunofluorescence showed epidermal intercellular deposition of IgG and complement component 3. Laboratory testing showed a desmoglein 1 level of 142 U/mL (reference range, <14 U/mL) and desmoglein 3 level of 150 U/mL (reference range, <14 U/mL). Liver and kidney function; routine blood and urine tests; and antinuclear antibody, hepatitis B and C antibodies, syphilis, and human immunodeficiency virus antibody levels were normal. The biopsy and immunofluorescence results combined with clinical feature were consistent with a diagnosis of pemphigus vulgaris (PV).

The patient initially was started again prednisone 50 mg daily, to which the skin eruptions responded, and 2 weeks later, the disease was considered controlled.

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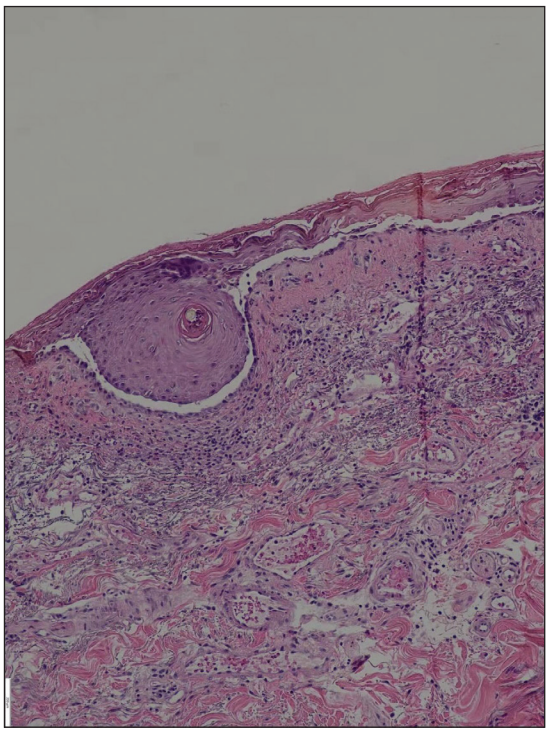

FIGURE 1. Biopsy of an early skin lesion on the trunk showed suprabasal acantholysis (H&E, original magnification ×100). Reference bar indicates 200 μm.

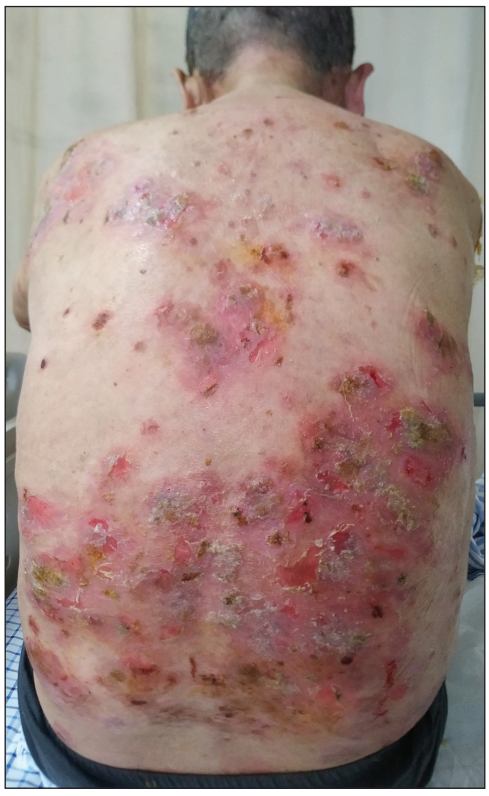

FIGURE 2. Pemphigus vulgaris. Crusted superficial erosions on the back.

The prednisone dosage was tapered to 20 mg daily 3 months later with no new blister formation. However, 2 weeks later, the patient was diagnosed by a tuberculosis specialist with pulmonary tuberculosis, and a daily regimen of isoniazid, rifampicin, ethambutol, and levofloxacin was instituted.

Ten days after starting antituberculosis therapy, the patient developed new erythematous blisters that could not be controlled and self-adjusted the prednisone dose to 50 mg daily. Two months later, blister formation continued.

Six months after the initial presentation, the patient returned to our hospital because of uncontrollable rashes (Figure 2). On admission, he had a Pemphigus Disease Area Index (PDAI) score of 32 with disease involving 30% of the body surface area. Laboratory testing showed a desmoglein 1 level of 233 U/mL and desmoglein 3 level of 228 U/mL. A tuberculosis specialist from an outside hospital was consulted to evaluate the patient's condition and assist in treatment. Based on findings from a pulmonary computed tomography scan, which showed the inflammation was considerably absorbed, treatment was adjusted to stop using ethambutol and levofloxacin and continue rifampicin and isoniazid. For the PV, prednisone was titrated upward to 75 mg daily, mycophenolate mofetil (MMF) 1 g twice daily was added, and IVIG 400 mg/kg daily was administered for 7 days. After 3 weeks, the rash still expanded.

In considering possible interactions between the drugs, we consulted the literature and found reports[1-3] that rifampicin accelerated glucocorticoid metabolism, of which the tuberculosis specialist that we consulted was not aware. Therefore, rifampicin was stopped, and the antituberculosis therapy was adjusted to levofloxacin and isoniazid. Meanwhile, the steroid was changed to methylprednisolone 120 mg daily for 3 days, then to 80 mg daily for 2 days.

After 5 days, the rash was controlled with no new development and the patient was discharged. He continued on prednisone 80 mg daily and MMF 1 g twice daily.

At 2-month follow-up, no new rash had developed. The patient had already self-discontinued the MMF for 1 month because it was difficult to obtain at local hospitals. The prednisone was reduced to 40 mg daily. Pulmonary computed tomography showed no signs of reactivation of tuberculosis.

Comment

The tuberculostatic compound rifampin induces expression of a number of drug metabolism-related genes associated with cytochromes (especially cytochrome P450 3A4), multidrug resistance (P-glycoprotein and multidrug resistance proteins 1 and 2), uridine 5′-diphospho-glucuronosyltransferase, monoamine oxidases, and glutathione S-transferases.

Drugs that depend on these enzymes for their metabolism are prone to drug interactions when

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co-administered with rifampicin.[4,5] It has been reported that rifampicin reduces the area under the concentration–time curve (AUC) of prednisolone by approximately 30% to 60%; some authors have suggested that, if rifampicin has to be prescribed, a 2- to 3-fold increase in the prednisolone dosage might be indicated.[1,4,6,7] Rifampicin also can influence immunosuppressive drugs in organ transplant recipients; for example, an 11-day course of rifampicin 600 mg daily was found to reduce the AUC of oral cyclosporine by approximately 70% and of intravenous cyclosporine by 28%.[4,8] Similarly, treatment with rifampicin 600 mg daily for 18 days reduced the AUC of oral tacrolimus by 68% and of intravenous tacrolimus by 35%.[4,9]

Rifampicin causes a marked reduction in dose-corrected mycophenolic acid exposure when administered simultaneously with MMF through induction of glucuronidation activity and inhibition of enterohepatic recirculation.[5,10] In in vitro studies, rifampin and other cytochrome P450 inducers have been identified as potentially useful for increasing the rate of cyclophosphamide and ifosfamide (an isomeric analogue of cyclophosphamide) 4-hydroxylation in the human liver in a manner that could have a favorable impact on the clinical pharmacokinetics of these anticancer prodrugs.[11] However, clinical analysis of 16 patients indicated that co-administration of ifosfamide with rifampin did not result in changes in the pharmacokinetics of the parent drug or its metabolites.[12]

The steroids and immunosuppressants mentioned above are widely used in the treatment of autoimmune diseases and drug hypersensitivity in dermatology. Drug interactions should be considered and drug concentrations closely monitored in cases of rifampin co-administration.

Conclusion

In our patient, the use of rifapentine resulted in a recurrence of previously controlled PV and resistance to treatment. The patient's disease was quickly controlled after discontinuation of rifampicin and with a short-term course of high-dose methylprednisolone and remained stable when the dosages of MMF and prednisone were reduced. This case serves as a reminder for clinicians to consider a drug interaction when treatment fails in order to avoid harming patients, especially those who have an autoimmune disease.

REFERENCES

1. Miyagawa S, Yamashina Y, Okuchi T, et al. Exacerbation of pemphigus by rifampicin. *Br J Dermatol*. 1986;114:729-732. doi:10.1111/j.1365-2133.1986.tb04882.x
2. Gange RW, Rhodes EL, Edwards CO, et al. Pemphigus induced by rifampicin. *Br J Dermatol*. 1976;95:445-448. doi:10.1111/j.1365-2133.1976.tb00849.x
3. Bergrem H, Refvem OK. Altered prednisolone pharmacokinetics in patients treated with rifampicin. *Acta Med Scand*. 1983;213:339-343. doi:10.1111/j.0954-6820.1983.tb03748.x
4. McAllister WA, Thompson PJ, Al-Habet SM, et al. Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J (Clin Res Ed)*. 1983;286:923-925. doi:10.1136/bmj.286.6369.923
5. Tavakolpour S. Pemphigus trigger factors: special focus on pemphigus vulgaris and pemphigus foliaceus. *Arch Dermatol Res*. 2018;310:95-106. doi:10.1007/s00403-017-1790-8
6. Barman H, Dass R, Duwarah SG. Use of high-dose prednisolone to overcome rifampicin-induced corticosteroid non-responsiveness in childhood nephrotic syndrome. *Saudi J Kidney Dis Transpl*. 2016;27:157-160. doi:10.4103/1319-2442.174198
7. Okey AB, Roberts EA, Harper PA, et al. Induction of drug-metabolizing enzymes: mechanisms and consequences. *Clin Biochem*. 1986;19:132-141. doi:10.1016/s0009-9120(86)80060-1
8. Venkatesan K. Pharmacokinetic interactions with rifampicin. *Clin Pharmacokinet*. 1992;22:47-65. doi:10.2165/00003088-199222010-00005
9. Naesens M, Kuypers DRJ, Streit F, et al. Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. *Clin Pharmacol Ther*. 2006;80:509-521. doi:10.1016/j.clpt.2006.08.002
10. Kuypers DRJ, Verleden G, Naesens M, et al. Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate–glucuronosyltransferase. *Clin Pharmacol Ther*. 2005;78:81-88. doi:10.1016/j.clpt.2005.03.004
11. Chenhsu RY, Loong CC, Chou MH, et al. Renal allograft dysfunction associated with rifampin–tacrolimus interaction. *Ann Pharmacother*. 2000;34:27-31. doi:10.1345/aph.19069
12. Douglas JG, McLeod MJ. Pharmacokinetic factors in the modern drug treatment of tuberculosis. *Clin Pharmacokinet*. 1999;37:127-146. doi:10.2165/00003088-199937020-00003

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