Herpes zoster in patients with peptic ulcer disease: a plausible association?

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In a recent paper Chen et al., using the longitudinal National Health Insurance Research of Taiwan database, compared 41,229 patients with peptic ulcer disease (PUD) and 41,229 matched controls. Because the cumulative incidence of varicella zoster infection in PUD patients was significantly higher compared with the control cohort ($P < 0.001$), the authors concluded that patients with PUD were at increased risk of herpes zoster (HZ) acquisition.¹

Apparently, there is no consistent plausibility to support this conclusion. *Herpesviridae* is a large family of DNA viruses that can cause diseases in humans. At least four species of *Herpesviridae* (herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV)) are documented to be widely spread among humans. The sites of latency are neurons for HSV and VZV, B cells for EBV and monocytes and lymphocytes for CMV.

It is well-known that *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs (NSAIDs) and *Herpesviridae* are involved in the pathogenesis of PUD or gastric erosions.² This family of viruses may be the cause of the disease in the pathogenesis of PUD or gastritis.³ Furthermore, VZV has been detected by polymerase chain reaction from endoscopic biopsy of subjects with common variable immunodeficiency.³ Nevertheless, it is difficult to prove the contrary. Chen et al. hypothesized that patients with PUD at a greater risk of varicella zoster infection due to their impaired cellular immunity and depressed nutritional status.⁴ However, there is no clear evidence that patients with PUD are immunocompromised. These patients are not more prone to infections than the general population.

It is well known that statistical associations may be causal, indirect or explained by artefacts. Indirect associations have sometimes been called self-selection because it has been hypothesized that persons predisposed to developing a certain disease have an unknown ‘X’ factor that automatically selects them to have the characteristics, thereby resulting in a statistical association.⁵ Artefacts can result from biased methods of selecting cases and controls. The major epidemiological problem in evaluating a statistical relationship is to determine whether or not the association is indirect and of aetiological significance. Randomized controlled experiments are generally recognized to be the gold-standard method for such assessment, but it is hard to see how these could be justified on ethical grounds.

References