Acral Papules: Gianotti-Crosti Syndrome

CASE STUDY:
A 3-year-old boy presents with a 2-month history of spreading papules, which began on his extremities. Review of systems is positive only for occasional pruritus. His mother denied any recent illnesses. He had been treated with triamcinolone ointment and an oral steroid taper, without benefit. Past medical history includes childhood seizures, chronic ear infections, asthma, and multiple allergies. Family history is positive for atopy.

Physical exam reveals multiple discrete monomorphic lichenoid 1- to 2-mm papules distributed on the arms, legs, face, and buttocks, with sparing of the abdomen, flexural surfaces, mucosal surfaces, palms, and soles (see Figure 1).

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DIAGNOSIS
Gianotti-Crosti syndrome (GCS)

DISCUSSION

First described by Ferdinando Gianotti in 1955 and then by Gianotti and Crosti 1 year later, Gianotti-Crosti syndrome is a unique cutaneous disorder characterized by the abrupt onset of an erythematous papular exanthem found on the extremities, buttocks, and face.

Initial descriptions of patients with an acrally located eruption along with lymphadenopathy, hepatomegaly, and anicteric hepatitis were considered to be of viral origin, and by the 1970s, hepatitis B virus (HBV) was thought to be the causative agent. Gianotti used the term “papular acrodermatitis of childhood” (PAC) to describe this syndrome, which he believed was solely a manifestation of hepatitis B infection. He also believed that a separate syndrome, papulovesicular acro-located syndrome (PAS), existed and could be distinguished clinically from PAC, with the papulovesicular variant being more pruritic, less monomorphic, and with a more prolonged course than PAC. He believed PAS was not caused by HBV but rather was a host response to a number of other infectious agents.

In 1992, a retrospective analysis of 308 cases seen between 1955 and 1989 in Gianotti’s Milan clinic was completed by Caputo et al. HBV had been confirmed in only 22.4% of these cases. This analysis showed that different etiologic varieties of papular and papulovesicular cases could not be distinguished based solely on cutaneous features. Caputo recommended the term “Gianotti-Crosti syndrome” to encompass both Gianotti’s papular acrodermatitis of childhood and papulovesicular acrolocated syndrome. This approach is now generally accepted.

Gianotti-Crosti syndrome has been reported worldwide, and Epstein-Barr virus (EBV) has become recognized as the most common viral agent associated with GCS. Cases of HBV-associated disease are now much more rare, likely in part caused by the increase in HBV vaccination programs. EBV, on the other hand, is a ubiquitous virus to which most children are exposed at a relatively young age and that correlates with the epidemiology of GCS found mainly in young children. Epidemics of GCS associated with both HBV and EBV have been reported.

GCS is mostly seen in young children between 1 and 6 years, with at least 30% of cases occurring within the first year of life. While it may last several weeks, the course is usually self-limited, and the rash will resolve within 3–4 weeks.

Lesions can be miliary, papular, or papulovesicular and are usually found on the upper trunk, face, and buttocks. Papules may heal with urticarial papules or papulovesicles, which may be slightly pruritic. Lesions can become confluent. Individual lesions range from 1 mm to 5 mm in diameter (lentil-sized), rarely exceeding 10 mm and are often flat-topped, occasionally edematous or with hemorrhage (purpuric), and less often with scale. The distribution is symmetrical and found on the cheeks, extensor surface of the extremities, and the buttocks, (see Figure 2). Papules usually begin on the thighs and buttocks, then spread to the extensor aspects of the arms, and finally to the face. Simultaneous appearance in all locations can be seen. Purpuric lesions are more common on the legs, in areas of trauma, and on the face after prolonged crying. The trunk, antecubital and popliteal surfaces, palms, soles, and mucosal surfaces are usually spared, but occasionally show lesions. Mild truncal involvement should not rule out GCS.

Lesions last for many weeks, and if only a few papules are present or atypical areas are involved, the diagnosis may be more difficult to establish. Lesions typically fade with mild desquamation in 3 to 4 weeks; a longer course
The eruption. As with lymphadenopathy, elevated liver enzymes may take a few months to return to normal. In hepatitis B-associated cases, viral markers are detectable in the serum early. The presence of the classic distribution and morphology of lesions should lead the practitioner to the correct diagnosis. The differential diagnosis includes lichen planus, Henoch-Schönlein purpura, erythema multiforme, pityriasis lichenoides, papular urticaria, frictional lichenoid dermatitis, lichenoid drug reaction, and id reaction. Biopsy is rarely necessary, and although findings are non-specific, histology may be helpful in ruling out other diagnoses.

Case reports over the past 50 years have demonstrated a large number of associated agents, including viruses, bacteria, and immunizations. A 2006 review cited viral cases of GCS associated with EBV; hepatitis A, B, and C; CMV; human herpesvirus 6 (HHV6); Coxackievirus A16, B4, and B5; rotavirus; parvovirus B19; molluscum contagiosum; respiratory syncytial virus (RSV); echovirus; mumps virus; parainfluenza; and HIIV. Bacterial associations include Bartonella henselae; beta hemolytic strep; Borrelia burgdorferi; and Mycoplasma pneumoniae. Reports of GCS occurring from 3 days to 1 month following immunizations including Japanese encephalitis; hepatitis A and B; DTP; Hib; MMR; oral polio; influenza; BCG; and diphtheria exist. Despite these reports, several large studies confirm that a causative agent is found in less than 50% of cases of GCS. A contributing factor is that many children are diagnosed clinically, and laboratory investigations are not undertaken. A study from Bologna, Italy, led by Ricci screened 29 children for a large but incomplete panel of infectious agents. Nine of 29 children had signs and symptoms of an associated infection but showed no microbiological evidence on testing. In general, the most common association is with viruses, with many case reports documenting the presence of viral antigen or antiviral antibodies in patient sera.

Interestingly, many of the children who developed GCS after receiving vaccinations were found to have clinically apparent or subclinical viral infections at the time of their immunization. A few studies clearly support the hypothesis of initial immunization followed by a viral infection as a possible mechanism for GCS. A 1994 epidemic of GCS secondary to EBV was described in Forti, Italy, and in those cases, prior vaccination with oral polio vaccine was a common event. Although the exact pathogenesis is still not currently understood, these cases suggest a pathway whereby the immune system is first primed, whether by immunization or other means.

Further evidence supporting an immune-mediated process is that GCS occurs more commonly in those with atopic dermatitis, but it is not clear if this is genetic or a specific pattern of reaction to many diverse stimuli. Assessing atopic background as a possible predisposing factor to help understand why exposure to different agents can lead to a similar clinical picture, Ricci and colleagues concluded that atopy may play an important role in conditioning the onset of the clinical papular eruption seen in GCS children exposed to various infectious agents. They added the hypothesis that atopic children may express a "papular prone" phenotype when exposed to various external stimuli, supported by reports of associated atopy with other papular dermatoses, such as frictional lichenoid eruption or lichen...
striatus. In our experience, a “papular prone” atopic phenotype is certainly consistent with atopic dermatitis or id reaction in pigmented skin.

In merging HBV and non-HBV cases and with different clinical pictures that vary include lymphadenopathy and hepatitis, some confusion can arise. Chuh and colleagues recently set out to define objective diagnostic criteria for the diagnosis of GCS. The goal of diagnostic criteria is to allow clinicians to objectively diagnose GCS and thereby reassure patients and parents of the benign course of the disease. In addition, criteria would allow further studies to be done and to be compared across cultures (see Sidebar).

The caveats are fourfold. On at least one occasion, all positive clinical features are seen; on all encounters, neither of the negative features are seen; none of the differential diagnoses are considered to be more likely than GCS clinically; and if biopsy is performed, findings are consistent with GCS. Chuh and colleagues showed that these criteria were applicable to children diagnosed with GCS in a private dermatology practice in India. The positive features were sensitive and were positively correlated with GCS, while the negative features were negatively correlated with GCS. It is important to remember that some truncal lesions do not exclude a diagnosis of GCS. There are also reports of GCS presenting with only facial papules, although such cases would not fit Chuh’s criteria.

There is no specific treatment for GCS. Oral antihistamines may be used for pruritus, and topical steroids have been used. There are reports of exacerbation of lesions secondary to the use of topical steroids. In our experience, this phenomenon is variable. The patient presented in this article did not improve or worsen with oral or topical steroids. However, topical steroids have been used in conjunction with antihistamines; a diagnosis of GCS should not deter the clinician from prescribing such medications. Treatment is usually unnecessary as the disease is self-limited. Patients with hepatitis B should be monitored and treated appropriately, and family members and close contacts may need screening. The prognosis is excellent. Active liver disease caused by hepatitis B in patients with GCS may regress without treatment, and only one fatality has been reported.

CONCLUSIONS
Viral exanthems are very common in childhood. As such, it is important for the general pediatrician to be able to recognize various exanthems to differentiate between harmless and self-limited ones and others that may be harmful to the patient or others around them (such as pregnant women and immunocompromised individuals). Gianotti-Crosti syndrome classically presents with an easily recognizable constellation of findings, which allows the astute clinician to reassure parents who may be understandably concerned for the welfare of their child. This is especially true because GCS may last for several months, typically longer than other viral exanthems of childhood. In atypical cases or those for which a differential diagnosis arises, a good history and physical exam, with particular attention to palpable liver or lymph nodes, simple laboratory investigations including HBV serologies and liver function tests, possible skin biopsy, and using the above criteria should help to differentiate Gianotti-Crosti syndrome from other childhood exanthems.

REFERENCES
15. Chuh AA. Truncal lesions do not exclude a diagnosis of Gianotti-Crosti syndrome. Aus