Cyclosporine-Induced Infantile Nodulocystic Acne

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Background: In adult organ transplant recipients, nodulocystic acne induced by the use of cyclosporine can be treated successfully with isotretinoin. Cyclosporine’s acnegenic effects in children and the pediatric response to treatment are less clear.

Observations: A 9-month-old boy presented with cysts and nodules on his face after he began cyclosporine therapy after a heart transplantation. We describe successful treatment with cessation of cyclosporine therapy and administration of isotretinoin.

Conclusions: Nodulocystic acne may be induced by the use of cyclosporine in children as well as adults. When it occurs, it can be managed with cessation of cyclosporine therapy and treatment with isotretinoin. Because this management approach may influence other outcomes in children with transplants, it is best to treat these patients using a multidisciplinary approach.

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Infantile acne, which often presents within the first 6 months of life and resolves spontaneously, is most commonly associated with fluctuations in circulating androgens that stabilize during the initial maturation of the adrenal gland. When prepubertal acne is persistent or nodulocystic, the clinician should consider other causes, such as hormonal aberrations (including tumors and hyperplasias), toxin exposures, and medications, including comedogenic topical products.

Pediatric organ transplant recipients are routinely maintained on a regimen of immunosuppressants, many of which have cutaneous adverse effects. One of the largest series to date that examined cutaneous adverse events in pediatric organ transplant recipients reported that all 145 children who received corticosteroids or cyclosporine had dermatologic adverse effects, including stria, acne, hypertrichosis, gingival hyperplasia, and cutaneous infections. We describe an infant with cyclosporine-induced nodulocystic acne that resolved after cessation of cyclosporine therapy and administration of isotretinoin.

A 9-month-old boy presented for evaluation of a new facial rash. He had a 6-week history of large red bumps on his cheeks that were tender, slow growing, and intermittently draining a yellowish fluid. His health was otherwise stable, with no evidence of lethargy, no change in eating habits, and normal development. Cultures of draining fluid were negative for bacteria, acid-fast bacilli, and fungi. Separate courses of oral cephalaxin and trimethoprim-sulfamethoxazole failed to result in improvement.

The patient’s medical history was remarkable for left hypoplastic heart syndrome, status post heart transplantation at 2 weeks of age. He had been maintained on a regimen of immunosuppressants (cyclosporine and azathioprine) since the transplantation but had not received systemic corticosteroids. His cardiovascular profile was stable according to routine echocardiograms, and cyclosporine levels were consistently within a therapeutic range.

Physical examination revealed multiple erythematous, fluctuant, tender cysts and nodules over both cheeks, with adjacent multiple smaller folliculocentric papules and pustules (Figure, A). The patient had no virilizing features with respect to hair growth, body habitus, or genitalia. A punch biopsy specimen showed a chronic deep folliculitis with abscess formation. Periodic acid–Schiff with diastase and acid-fast bacillus stains were negative for fungal elements and myco-
bacteria, respectively. Tissue cultures showed only normal bacterial flora. Serum dehydroepiandrosterone sulfate and free testosterone levels were within normal limits. The patient underwent congenital adrenal hyperplasia screening at birth and at 2 weeks of life, with a normal serum 17-hydroxyprogesterone concentration; no additional endocrine studies were performed.

A diagnosis of nodulocystic acne due to cyclosporine therapy was made. After we discussed the case with the transplantation team, the cyclosporine therapy was discontinued and tacrolimus therapy was initiated. Isotretinoin therapy (0.5 mg/kg) was initiated concomitantly; 10-mg capsules were lanced and mixed into chocolate pudding for oral administration every other day. With the aim of aggressive treatment to lessen scarring potential, a brief course of oral corticosteroids (prednisolone phosphate, 1 mg/kg/d) was also administered during the first month of isotretinoin therapy. The patient’s acne dramatically improved within the first 24 to 72 hours after the cyclosporine therapy was discontinued, and he showed continued improvement during the isotretinoin therapy (Figure, B and C). He completed a 5-month course of isotretinoin, for a cumulative dose of 114 mg/kg. The results of his blood work were coordinated with his transplantation team to minimize venipuncture episodes on a monthly basis. With the exception of a transient leukopenia (from 5500 to 3300 cells per microliter) that resolved after the first month of treatment, his blood indexes (including a complete blood cell count with differential, a comprehensive metabolic panel, and a fasting lipid profile) were normal throughout treatment. His course was complicated by xerosis and retinoid dermatitis, which was treated effectively with topical fluocinolone acetonide, twice daily as needed.

Cyclosporine, which is an inhibitor of T-lymphocyte activation that is used routinely during the management of solid organ transplants, can cause a variety of cutaneous adverse reactions. One study of 67 adult renal transplant recipients who were treated with cyclosporine showed that most of the cutaneous adverse effects involved the pilosebaceous unit: hypertrichosis (60%), epidermal cysts (28%), keratosis pilaris (21%), acne (15%), folliculitis (12%), and sebaceous hyperplasia (10%). In vitro studies have suggested that follicular epithelium is more sensitive to the growth-promoting effects of cyclosporine than are interfollicular keratinocytes.

The first cases suggesting an association between cyclosporine and nodulocystic acne were reported in the late 1980s and early 1990s. Most reports describe adult patients with heart and renal transplants who developed nodulocystic acne and were treated successfully with isotretinoin. However, some patients have improved with cessation of cyclosporine therapy alone. While an association between cyclosporine use and acne now appears clear, causality remains to be established, particularly given the lack of reported rechallenges with cyclosporine.

Whether children develop similar cutaneous reactions from cyclosporine use as adults is not completely clear. Hypertrichosis and gingival hyperplasia represent most dermatologic complaints in the pediatric population. One small series reported that all cyclosporine-treated pediatric renal transplant recipients had cutaneous adverse effects, mostly hypertrichosis. Another study showed that gingival hyperplasia occurred more frequently in children than in adults. Age may alter the manifestation of these reactions. For example, one series demonstrated that younger children had more severe adverse effects than older children. The same series showed that acne tended to occur in older children, with no cases of acne in patients younger than 2 years. Because infants were underrepresented in all of these series, it is difficult to assess their true risk of cyclosporine-induced adverse effects.

Regardless of association with cyclosporine use, infantile nodulocystic acne should be treated aggressively. Isotretinoin has demonstrated success in the treatment of nodulocystic infantile acne. It should be noted that multiple interventions were undertaken simultaneously for our patient (cessation of cyclosporine therapy, initiation of isotretinoin therapy, and administration of a short burst of prednisone), and it is unclear which one contributed most to his improvement.

When contemplating treatment with systemic retinoids for similar patients, health care providers should recognize that transplant recipients may be at risk for unique adverse events, such as graft rejection and disrupted bone growth. Studies examining retinoid effects on graft rejection show mixed observations, with some suggesting detriment and others suggesting benefit. Regarding effects on bone, transplant recipients may have a higher risk of adverse effects because of several contributing factors, such as administration of systemic corticosteroids, prolonged bed rest, and frequent hospitalizations. While retinoid use has been associated with adverse effects on bone in children, most data are retrospective and involve long-
term therapy with etretinate for disorders of keratinization.\textsuperscript{17} Other case reports document long-term use with no adverse bone effects.\textsuperscript{18} Therefore, the potential for disrupted bone metabolism in the transplant population is unclear, and the dermatologist should work with the transplant team to detect and manage these events.

In summary, we present a pediatric case of cyclosporine-induced nodulocystic acne that was successfully treated with cessation of cyclosporine therapy and a 5-month course of isotretinoin (114 mg/kg). Isotretinoin capsules can be lanced and mixed with food for ease of administration to infants. Our patient remains acne-free 8 months after the completion of isotretinoin therapy and on an alternative effective immunosuppressive regimen. This case illustrates the importance of a multidisciplinary approach when managing severe medication-induced cutaneous adverse effects.

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REFERENCES


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