

**Figure 2.** Change in mean combined visual analog scale score (VAS) (range, 0-100 mm) over the course of treatment with timolol maleate, 0.5%, gel.

and +100, complete shrinkage). Descriptive statistics and the observer intraclass correlation were performed.

**Results.** The **Table** lists patient characteristics and response data. Clinically, 3 patients had IHs still in the proliferative phase; 2 had IHs that were stable; and 1 had IHs in regression. The difference in appearance of IHs at the various stages of treatment is shown in **Figure 1**. The mean change in VAS over time is presented in **Figure 2**. None of the patients experienced any local or systemic adverse events.

**Comment.** This proof of concept study shows that timolol maleate, 0.5%, gel, a nonselective  $\beta$ -blocker in topical formulation, is effective and safe for the treatment of IHs. Patients with superficial IHs and those treated for longer periods showed better response to timolol. Early intervention during the rapid proliferative phase (age 1-6 months) may result in better and faster resolution of IHs. This preliminary work suggests that topical timolol maleate, 0.5%, gel is an alternative to systemic propranolol for treatment of superficial IHs. Further prospective studies are required to substantiate the safety and efficacy of timolol maleate, 0.5%, gel in the treatment of IHs.

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## Anetoderma of Prematurity: An Iatrogenic Consequence of Neonatal Intensive Care

**A**netoderma of prematurity was described by Prizant et al<sup>1</sup> in very-low-birth-weight infants in neonatal intensive care units (NICUs). This recent description probably reflects improvement in care of premature neonates who were previously unable to survive. The mechanism for the development of anetoderma is unknown, but the role of monitoring leads has been suspected. To further delineate this clinical condition, we have studied 11 additional cases.

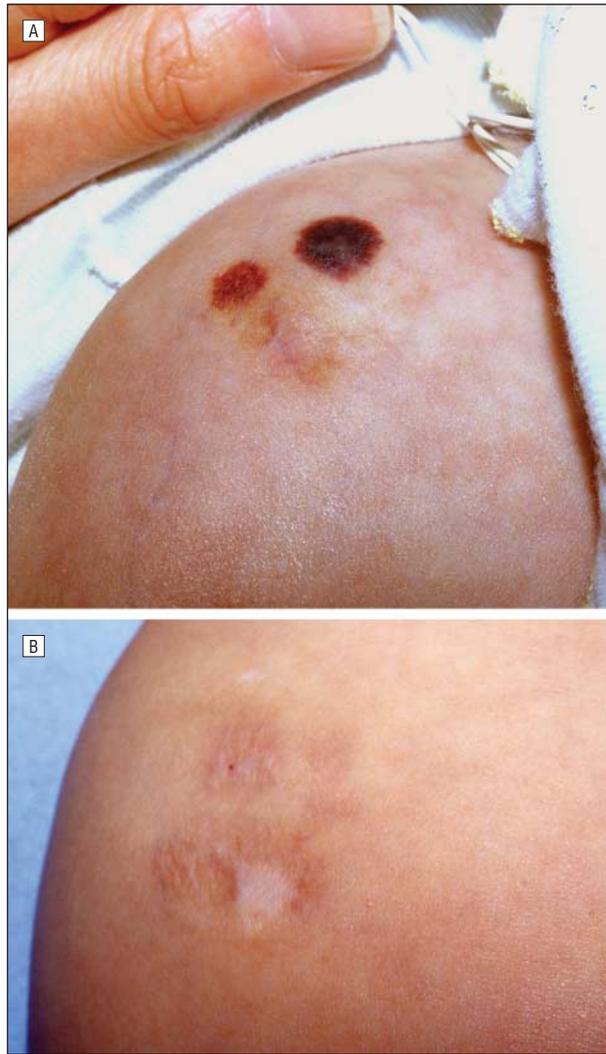
**Methods.** All cases of anetoderma of prematurity seen in a single NICU (University Hospital, Dijon, France) from 1999 to 2006 were retrospectively studied. Anetoderma was diagnosed clinically.

**Results.** Gestational age and birth weight ranged from 25 to 30 weeks and from 725 to 1250 g, respectively. All neonates had pulmonary diseases and required assisted ventilation. Ten developed bronchopulmonary dysplasia and received oral steroid treatment. Three had severe digestive tract complications (necrotizing enterocolitis or ileal perforation). Nine were treated with indomethacin for patent ductus arteriosus, and 4 of these needed surgical closure. The median duration of hospitalization in the NICU was 125.0 days vs 99.5 days in 30 control neonates matched for gestational age ( $P = .001$ ).

Twin pregnancies occurred in 5 cases, but no cotwins were affected with anetoderma. In these twin pairs, the affected twin had the lower birth weight in 2 instances, and the higher in 3 instances. The incidence and severity of pulmonary or digestive tract diseases were similar in twins without anetoderma.

Localized, rounded flat, atrophic skin patches 5 to 20 mm in diameter were first noted between age 6 weeks and 5 months (**Figure 1B** and **Figure 2A**). Five infants had previously been examined for ecchymoses without atrophy or necrosis (**Figure 1A**) at the sites where monitoring leads had been applied. On follow-up, all ecchymoses turned into atrophic patches within a few days. Previous placement of monitoring leads at the site of atrophic patches was noted in 8 cases. All lesions were ventrally located: in the subclavicular areas on the chest in 8 cases (**Figure 1**) and in paraumbilical areas on the abdomen in 6 (**Figure 2**).

Follow-up data were available for 8 infants. All atrophic patches evolved into typical herniated anetoderma (Figure 2B and C). No self-healing or improvement occurred. In 1 child aged 7 years, persistent anetoderma le-



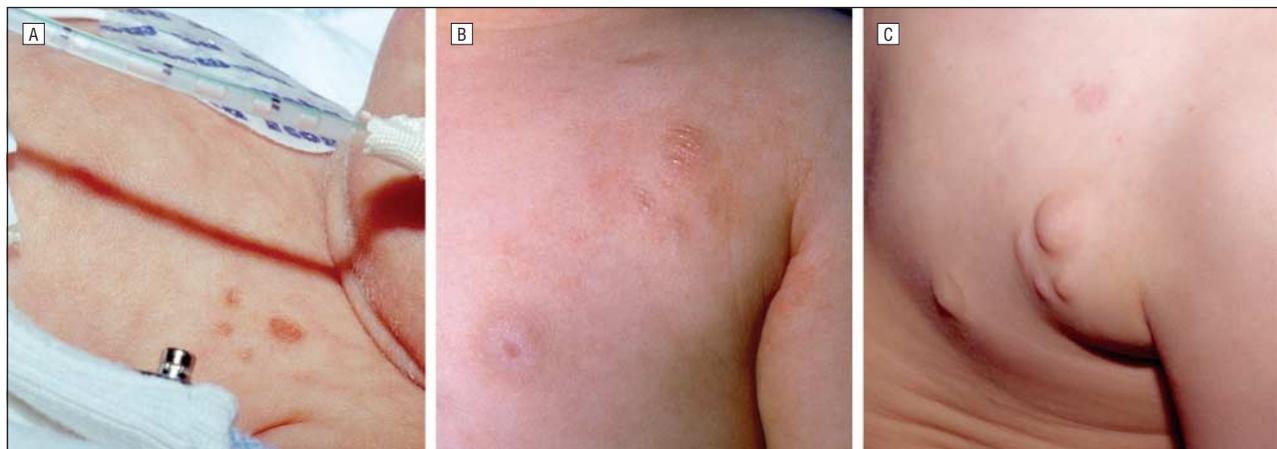
**Figure 1.** The periumbilical region of patient 3. A, Initial ecchymosis (age 4 months). B, Late atrophic patches (age 16 months).

sions on the upper chest caused disfigurement and led to surgical excision.

Eight cases were observed in a 2-year period between 1999 and 2001. At that time, because the pressure of the monitoring leads was suspected to be a causative factor, a preventive approach was implemented in the NICU. Monitoring leads were always applied on the ventral side when the infants were lying supine and on the dorsal side when lying prone, thus avoiding pressure from the leads onto the skin caused by the infants' weight. From that day on, only 3 additional cases were seen in the following 5-year period between 2001 and 2006.

**Comment.** Anetoderma of prematurity has rarely been reported.<sup>1-4</sup> Although ascertained at a single institution, the number of cases in our series, to our knowledge, is the highest ever reported. This suggests that the condition has previously been underreported. Birth weight does not appear to play a significant role,<sup>2</sup> as suggested by our 5 discordant twin pairs. Most cases developed at the site of monitoring leads, where ecchymoses had sometimes been noted. From this we conclude that monitoring leads likely play a causative role, although the precise mechanism remains unknown.<sup>1</sup> The hypothesis of local hypoxemia due to pressure on immature skin is strengthened by the decreased incidence of anetoderma following postural prevention. However, another explanation might be excessive traction on the skin when adhesive electrodes are removed, insufficient for skin tearing but causing either subclinical dermal damage or visible ecchymosis leading to anetoderma. Indeed, involvement of the periumbilical area suggests the role of adhesive tapes used for attachment of umbilical arterial lines. Hence, anetoderma of prematurity likely results from unnoticed minor iatrogenic trauma in the NICU, where cutaneous injuries are among the most common iatrogenic events. The prolonged duration of hospitalization supports this hypothesis. Anetoderma of prematurity is thus acquired and should be differentiated from congenital anetoderma, which is of unknown origin and has also been described in premature neonates.<sup>5</sup>

Because anetoderma patches tend to persist, they might cause long-lasting disfigurement on visible sites such as



**Figure 2.** The left subclavicular region of patient 5. A, Ecchymotic macules (age 6 weeks). B, Atrophic patches (age 9 months). C, Anetoderma with herniation (age 24 months).

the upper chest. Thus, they should be prevented by avoiding placement of leads in this area. When anetoderma patches are first encountered later in childhood, their diagnosis may be difficult, and a neonatal history of extreme prematurity and a NICU stay can be a helpful clue.

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## COMMENTS AND OPINIONS

### Antioxidant Supplementation and Risk of Skin Cancers

In a recent analysis of the VITAL (VITamins And Lifestyle) study cohort,<sup>1</sup> Asgari et al<sup>2</sup> failed to identify an association between antioxidant supplementation and the risk of incident melanomas. On this basis, they question the association previously observed in the SU.VI.MAX study (Supplementation en Vitamines et Minéraux Antioxydants).<sup>3,4</sup> However, the 2 studies do not address the same question. The SU.VI.MAX study was a pro-

spective randomized clinical trial testing the hypothesis that supplementation would influence cancer risk.<sup>4</sup> The VITAL study was an observational study testing the hypothesis that individuals who use antioxidant supplementation would differ in their cancer risk from those who do not. The reasons why this does not directly address whether supplementation influences cancer risk are clearly explained in the discussion of the original article describing the VITAL study.<sup>1</sup> The individuals who used supplementation may have had a healthier lifestyle or cultivated more health-oriented behavior than those who did not. For example, those using supplementation also exercised more and had a lower body mass index and a healthier diet. Although these confounders can to some extent be accounted for in the risk determination, and certain confounders were indeed included in the reported analysis, the 2 populations are different. It is thus impossible to attribute any difference observed to supplementation or to inherent between-group differences. The only way to study supplementation reliably is through a randomized prospective study where between-group differences are minimized through randomization. This was the strategy pursued in the SU.VI.MAX study. In addition, failure to reject the null hypothesis (no difference between groups) in the VITAL study analysis does not mean that no such difference exists but only that one was not observed (absence of proof is not the same as proof of absence).

Asgari et al<sup>2</sup> also make 2 statements about the SU.VI.MAX study<sup>4</sup> that are misleading and that we would like to rectify. First, they state that melanoma risk factors were not recorded in the SU.VI.MAX study. This is incorrect: participants completed 2 questionnaires including a number of items related to lifetime and previous-year sun exposure, and skin phototype was determined at the first medical visit. These factors did not differ between groups (consistent with the randomization) and thus cannot explain the difference in melanoma risk observed.

Second, Asgari et al<sup>2</sup> suggest that case ascertainment could be incomplete. However, care was taken to optimize ascertainment by collecting data from multiple sources, including the participants themselves, primary care physicians, hospital records, and laboratory test results, all reviewed by an expert adjudication committee. Indeed, the number of cases identified is consistent with the known incidence of skin cancers in the French general population.

Asgari et al<sup>2</sup> rightly point out that the confidence limits of the incidence rates determined in the SU.VI.MAX trial are wide owing to the low number of incident cases. However, the only way to improve the precision of the estimate of the skin cancer risk associated with antioxidant supplementation would be to perform an even larger or longer randomized clinical trial. In contrast, observational studies cannot address this issue adequately.

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