

clude that the process of melanoma tumor growth and metastasis is a complex, multistep cascade that is probably influenced by the variable expression of α_4 integrins at different stages in the cascade. Perhaps α_4 expression is protective of melanoma-cell detachment early in the cascade but harmful later by promoting metastasis. Regardless, we recommend that clinicians strongly consider alternative therapies or, at a minimum, surveillance strategies for patients at high risk for melanoma for whom natalizumab therapy is planned, at least until further data are available.

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Peculiar Morphology of Stones in Primary Hyperoxaluria

TO THE EDITOR: Primary hyperoxaluria type 1 is a rare inherited disease leading to recurrent nephrolithiasis, nephrocalcinosis, systemic oxalosis, and renal failure, ultimately requiring combined kidney and liver transplantation.^{1,2} Because of the rarity of this disorder, the diagnosis is often missed or delayed by several years, especially when the disease first manifests in adulthood, thus depriving patients of the benefits of therapeutic measures that have been instituted in a timely manner.^{2,3} Therefore, any method allowing early diagnosis is eagerly awaited.⁴ However, although nephrolithiasis is the revealing symptom in the great majority of patients with this disease at any age, until now little attention has been paid to the analysis of stones as a possible diagnostic tool.

Over the past 20 years, we analyzed stones obtained from 74 patients with a diagnosis of primary hyperoxaluria type 1 established on the basis of complete urinary biochemical tests and evidence of an enzyme defect. In addition to findings on infrared spectroscopy, we examined the morphologic characteristics of the surface and sections of calculi by means of a stereomicroscope.⁵ All primary hyperoxaluria type 1 calculi were composed of pure or virtually pure (>95%) calcium oxalate monohydrate, or whewellite. As compared with idiopathic calcium stones with a similarly high whewellite content, all primary hyperoxaluria type 1 calculi showed very peculiar morphologic characteristics, including a whitish

or pale-yellow surface and a loose, unorganized section, quite different from the dark-brown surface and well-organized, radiating inner structure of common whewellite stones (Fig. 1). In addition, scanning electron microscopy confirmed a crystalline structure in the primary hyperoxaluria type 1 stone that was distinct from that of the common type of whewellite stone. This unique morphologic characteristic and the ultrastructure of primary hyperoxaluria type 1 stones suggest a fundamental difference in the mechanism of stone formation, reflecting the very rapid and permanent crystal formation induced by genetic hyperoxaluria. The peculiar morphologic charac-

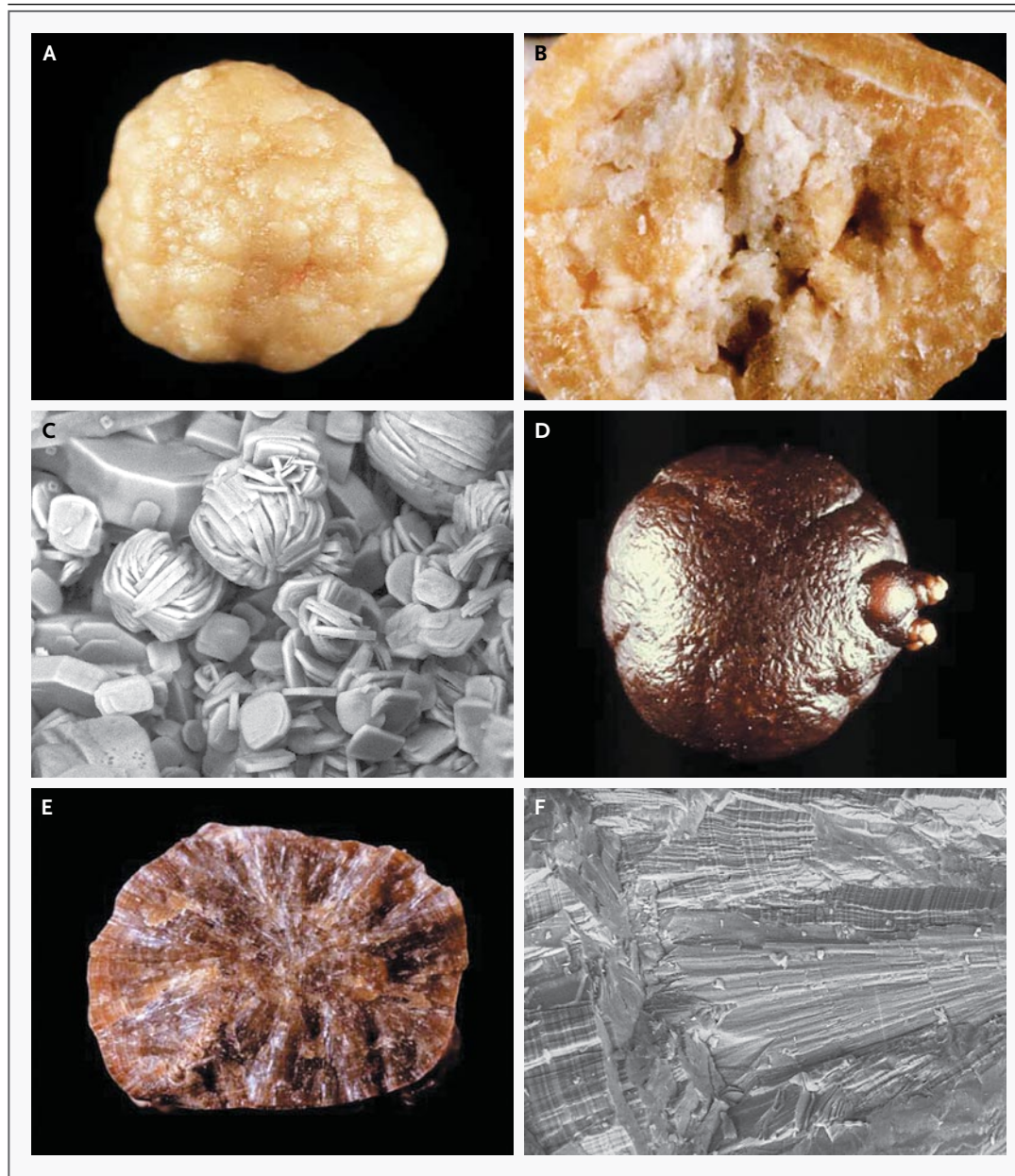
Figure 1 (facing page). Morphologic Characteristics of a Whewellite Stone in Typical Primary Hyperoxaluria Type 1 and of a Typical, Idiopathic, Common Type of Whewellite Stone.

Panels A, B, and C show a typical whewellite stone from a patient with primary hyperoxaluria type 1. Panels D, E, and F show a typical, idiopathic, common type of whewellite stone. Panels A and D show the stone surfaces on stereomicroscopic examination. Panels B and E show the sections on stereomicroscopic examination, and Panels C and F show the sections on scanning electron microscopy. There is a marked difference between the dense, radiating charcoal-like structure of the common type of stone, and the inhomogeneous, loose structure of the primary hyperoxaluria type 1 stone, with crystal aggregates of various sizes and shapes including curious, characteristic spherical structures of about 50 μm in diameter resembling balls of wool.

teristics of stones consistently observed in patients with primary hyperoxaluria type 1 (and in the two patients with primary hyperoxaluria type 2 whose stones were analyzed at our laboratory) appeared to be pathognomonic for this cause, since it was never observed in patients with other hyperoxaluric states (including 45 patients with enteric hyperoxaluria) or in any patient in whom a calcium stone formed without hyperoxaluria.

Therefore, such appearance of stones might be a valuable indicator of primary hyperoxaluria type 1, prompting early comprehensive laboratory evaluation, including measurements of urinary oxalate, glycolate, and glycerate in order to achieve a definitive diagnosis.

On the basis of our positive clinical experience, we propose that a morphologic examination be performed before compositional analysis by means



of x-ray diffraction or infrared spectroscopy, since this direct examination constitutes a simple, rapid, and cheap tool that might point toward the early diagnosis of primary hyperoxaluria type 1. This diagnosis might provide affected patients with a better chance to benefit from the early institution of adequate therapeutic management and might prevent, or substantially retard, the consequences of this devastating disease.

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