A 4-year-old, previously healthy boy presented to the emergency department with a 2-day history of polydipsia, fatigue, irritability, cheilitis and a refusal to bear weight. One month previously, he had had an episode of similar symptoms, which had resolved. His vital signs, height (102.4 cm), weight (16.7 kg) and body mass index (15.9 kg/m²) were normal (Box 1). He appeared pale, with significant cheilitis, xerotic skin, diffuse alopecia and periorbital and pedal edema (Figure 1). Initial investigations were significant for severe hypercalcemia, hyponatremia, hypokalemia, mildly elevated creatinine, elevated C-reactive protein, leukocytosis and normocytic anemia (Box 1). Abdominal ultrasound showed bilateral pelves and medullary nephrocalcinosis. We admitted the patient to hospital and started hydration with intravenous (IV) fluids.

Initial investigations showed an appropriately low parathyroid hormone and 1,25-dihydroxyvitamin D (1,25(OH)₂D), with a normal thyroid-stimulating hormone level. We also ordered tests for parathyroid hormone-related peptide, vitamin A and 25-hydroxyvitamin D (25[OH]D) levels. Skeletal radiographs identified diffuse osteopenia, and periosteal reactions along the ribs, both radii and clavicles. Magnetic resonance imaging of the brain, spine and chest identified grade 3 papilledema, for which the patient was started on acetazolamide. He also had elevated liver enzymes, a prolonged international normalized ratio and hypoalbuminemia. A liver ultrasound showed hepatomegaly, and abnormal shear wave elastography was suggestive of fibrosis. Serum and urine toxicology screen, and viral (cytomegalovirus, Epstein–Barr virus and hepatitis A, B and C) and autoimmune hepatitis workup were negative.

While in hospital, our patient developed persistent and worsening bicytopenia, with low platelets and hemoglobin necessitating a blood transfusion. A workup for malignant disease, including bone marrow aspirate with flow cytometry, as well as urine vanillylmandelic acid and homovanillic acid, were negative. Despite being afebrile with normal vital signs and negative blood cultures, the patient had persistently elevated inflammatory markers, which gradually reduced without treatment.

After the patient had spent 2 weeks in hospital, we received the results of his outstanding investigations (Box 1). His parathyroid hormone-related peptide and total 25(OH)D levels were normal, but the vitamin A level was significantly elevated at 4.1 (reference 1.0–1.6) µmol/L. Because of his elevated vitamin A level, we carefully reviewed his diet and supplement intake. He was on a predominantly plant-based diet, and we estimated his vitamin A intake to be 3500–7000 international units (IU) per day, or 400–800 µg/d RAE. We referred to the US Department of Agriculture to provide the levels of vitamin A in the foods (https://fdc.nal.usda.gov/) and the conversion of factors for RAE and IU from the US National Institutes of Health (Box 2). The patient’s main sources of vitamin A included 1–2 cups of kale, 2–3 cups of green vegetables, 2–3 cups of fruit and 4 oz of meat per day (nonliver), plus a multivitamin containing vitamin A as β-carotene (28 µg RAE). He had previously been taking cod liver oil supplements (276 µg/d RAE) for more than 1 year, but had stopped many months previously.

We managed the patient’s hypercalcemia with IV hydration, multiple doses of subcutaneous calcitonin and IV bisphosphonates and a low vitamin A diet (Figure 2). We discharged him home with a normal ionized calcium, and 1 month after discharge, his hypercalcemia and bicytopenia had resolved. His papilledema improved and he was tapered off acetazolamide. His liver markers remain mildly elevated, with ongoing evidence of fibrosis on liver ultrasound. Five months after discharge, the patient sustained a femoral fracture from a fall from standing height.
We present a case of a 4-year-old boy with hypercalcemia and classic cutaneous features of vitamin A toxicity, including dry skin, cheilitis and alopecia.\(^1\) He also had commonly reported symptoms of vitamin A toxicity (i.e., fatigue, anorexia, pruritis, headache and bone pain) and clinical features (i.e., nephrocalcinosis, pseudotumour cerebri and liver toxicity).\(^1\) He had a low level of parathyroid hormone, low 1,25(OH)\(_2\)D, normal 25(OH)D, and normal parathyroid hormone-related peptide, which helped to narrow the differential diagnosis for hypercalcemia (Figure 3). Ultimately, his vitamin A level was 2.5 times greater than the normal range, which was likely caused by high vitamin A intake.

Vitamin A can be consumed either as preformed vitamin A, in the form of retinol found in animal sources (e.g., meat, liver, liver oils), some multivitamins and fortified foods (e.g., milk, butter, cereals), or as provitamin A (\(\alpha\)- or \(\beta\)-carotene), found in fruits and vegetables (e.g., kale) and some multivitamins\(^3\) (Box 2). Vitamin A quantities are measured using RAE, with 1 RAE equal to 1 µg retinol. It is thought that toxicity cannot be reached with provitamin A foods, as the efficiency of intestinal absorption falls as intake increases and conversion of carotenoids to retinol is regulated.\(^4\) No pediatric...
cases of toxicity have been associated with provitamin A, whereas toxicity from preformed vitamin A has been reported with acute ingestions exceeding 200,000 IU/day over the course of days, and chronic ingestions of 1500 IU/kg/day over months to years.

Our patient was ingesting 1850–3780 IU/kg/day of predominantly provitamin A for years. While children can develop toxicity at lower total doses of preformed vitamin A than those required to cause toxicity in adults, our case is somewhat unusual in that the patient was consuming large quantities of provitamin A from fruits and vegetables, notably kale. One explanation is that intake of large quantities of provitamin A and preformed vitamin A from cod liver supplements together may have caused toxicity, as the effect of high levels of preformed vitamin A on the metabolism of provitamin A may be synergistic.4

Dietary recall is fraught with difficulty, especially with children. Even in optimal circumstances, parents may be uncertain about the dose or duration of supplementation, or inadvertently overlook other supplements.

Vitamin A storage and metabolism is complex. The liver stores 80% of the body’s vitamin A and is susceptible to toxic doses.

### Box 2: Common food sources of vitamin A described in units of vitamin A per serving

| Food                  | Vitamin A per serving |
|-----------------------|-----------------------|
|                      | IU  | µg RAE          |
| Raw mango, 1          | 2240 | 112             |
| Raw red pepper, 0.5 cup | 2332 | 117            |
| Raw cantaloupe, 0.5 cup | 2706 | 135           |
| Fortified cereal, 1 cup | 500  | 149            |
| Cooked kale, 0.5 cup  | 8854 | 443             |
| Raw carrots, 0.5 cup  | 9189 | 459             |
| Boiled spinach, 0.5 cup | 11458 | 573       |
| Sweet potato in skin, 1 | 28058 | 1403        |
| Beef liver, 3 ounces  | 22175 | 6582        |

Note: IU = international units, RAE = retinol activity equivalents. *Recommended dietary allowances for vitamin A range from 400 to 900 µg RAE/d, based on age. Source: National Institutes of Health, Office of Dietary Supplements (https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/).

### Figure 2: Trend in patient’s ionized calcium (mmol/L) and vitamin A (µmol/L) levels over time from date of initial presentation to hospital (days), with treatment for hypercalcemia with calcitonin, pamidronate and zoledronate, indicated by the green, yellow and purple arrows, respectively. The dotted lines along the ionized calcium and vitamin A levels indicate levels from time of discharge (at 31 d) to first follow-up (54 d). The horizontal blue line indicates the upper limit of normal for ionized calcium, and the horizontal red line indicates the upper limit of normal for vitamin A.
therefore, liver diseases such as viral hepatitis and cirrhosis may increase susceptibility to vitamin A toxicity and worsen liver damage. In 1 study of 41 mostly adult cases of vitamin A hepatotoxicity, some developed cirrhosis with doses as low as 25 000 IU/day. Therefore, it is possible that liver damage from vitamin A toxicity from preformed vitamin A could have affected our patient’s ability to appropriately regulate high intakes of provitamin A. Although viral and autoimmune workup for liver disease was negative, we did not do a liver biopsy, so we cannot definitively rule out liver disease from another cause.

Vitamin A is also stored in the kidneys and adrenal glands and excreted partly in urine. Our patient had mild pre-renal acute kidney injury secondary to hypercalcemia, which may have reduced vitamin A clearance and exacerbated toxicity. Other factors that modulate vitamin A potency include low-protein diets, chronic kidney disease and concurrent use of certain vitamins, such as vitamin D and E, none of which were pertinent in this case. Furthermore, heritable variability in vitamin A metabolism is known, which may explain why toxicity occurs at a wide range of intakes. Interestingly, our patient had a 6-year-old brother who was consuming a similar diet, yet did not develop symptoms of vitamin A toxicity.

Our case may be of relevance to families shifting to plant-based diets and using vitamin supplements on a regular basis. Short-term dietary studies have shown that as much as 75% of the general population is ingesting more than the recommended daily allowance of vitamin A, mostly in the preformed form. Only a fraction of consumers discuss with their physicians their use of dietary supplements such as vitamins. Our case describes an extreme presentation, but patients may present with milder symptoms of vitamin A toxicity, which may be overlooked or dismissed as vague and nonspecific.

Vitamin A toxicity is an important diagnosis to consider in patients with hypercalcemia. Although our patient had classic findings of vitamin A toxicity, his case had unique features that made the diagnosis challenging, including toxic ingestion with predominantly provitamin A rather than preformed vitamin A, refractory hypercalcemia and bicytopenia despite a normal bone marrow biopsy. Chronic vitamin A toxicity is particularly challenging, as toxicity may occur at what people perceive as a “safe doses” of vitamin A from dietary sources and supplementation.
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