Journal of
Medical Case Reports

CASE REPORT

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A mixed immediate and delayed allergy to oral vitamin D supplementation: a case report

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Abstract

Background Vitamin D deficiency is common worldwide and of particular concern for populations at higher latitudes, including those in developed areas such as Australia. The role of vitamin D in modulating bone health and the immune system is well recognized. Patients frequently have vitamin D deficiency identified and managed in the primary healthcare setting. Despite the high prevalence of use in Australia, allergies to supplemental vitamin D are uncommon.

Case presentation The case presented here is a 53-year-old Caucasian female of Northern European ancestry, with a history of asthma and irritable bowel syndrome who was prescribed supplemental vitamin D. She experienced dyspepsia and stomach cramps within minutes of ingesting a vitamin D supplement. An alternative formulation of vitamin D produced similar gastrointestinal effects, worsening asthma and a rash. The results of the investigations were unremarkable except for mildly elevated total immunoglobulin levels. The patient was referred to an allergy clinic where a diagnosis of vitamin D hypersensitivity, with features of both immunoglobulin-E-mediated (type 1) and T-cell (type 4)-mediated pathways, was made. A desensitization program was commenced using a modified Australian protocol. During the 18-week course, the patient was exposed to increasing doses of vitamin D, and after 6 months, a daily dose of 1000 IU was tolerated. She continues to use daily antihistamines and avoids foods rich in vitamin D.

Conclusion This case report highlights a rare likely allergic reaction to supplemental vitamin D. The patient was never known to have supratherapeutic levels of vitamin D, but her history of atopy may increase the likelihood of an immune-mediated response to the supplement. While skin sensitivity testing was negative, a provocation test and the Naranjo scoring system indicated that a "probable" allergy occurred. Vitamin D deficiency is easily detected in primary healthcare, and oral supplementation is usually a safe and effective means to restore blood levels. While reactions to vitamin D supplementation in normal doses are rare, an allergic cause should be considered when there are no other likely precipitants. Personalized, carefully supervised, desensitization to vitamin D may enable the resumption of supplementation and help prevent unnecessary morbidity and mortality from vitamin D deficiency.

Keywords Primary care, Vitamin D, Desensitization, Allergy

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Background

Vitamin D deficiency is a common problem worldwide [1]. Even for high-income countries such as Australia, vitamin D deficiency remains relevant because populations at low latitudes receive less sun exposure than do those closer to the equator. High rates of vitamin D deficiency in Australia pose a risk for the aging population. Although 23% of the adult population has lower than recommended vitamin D levels, only 5% take a supplement [2]. These findings suggest that many Australians could be recommended some form of vitamin D in the future.

Vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are forms of vitamin D derived from ultraviolet light-mediated activation of dietary plant steroids (ergosterols) and sterol precursors in the skin, respectively [3–5]. The main form of vitamin D in circulation is 25-hydroxyvitamin D [25(OH)D], which is formed by the activation of vitamins D3 and D2 in the liver [6]. The biologically active form of vitamin D (calcitriol) is formed by the hydroxylation of 25(OH)D to $1,25(OH)_2D$ in the kidneys [3, 4].

Dietary sources of vitamin D (oily fish, eggs, and meat) are usually insufficient to achieve the recommended daily adequate intake for adults aged 51–70 years (400 IU) or aged over 70 years (600 IU) [7]. Skin color, the amount and duration of skin exposure to the sun, and geographical location further influence *in vivo* vitamin D production [6].

Low levels of 25(OH)D have been associated with increased risks of cardiovascular, respiratory, gastrointestinal, neurological, metabolic, and skin conditions and cancer [8]; however, vitamin D deficiency is most commonly associated with the risk of bone disease [7, 9]. Vitamin D promotes calcium absorption from the small intestine, reduces parathyroid hormone synthesis and secretion, and promotes bone mineralization [6]. Although less common than the sequelae of low vitamin D levels, vitamin D supplementation, especially if excessive, has the potential to cause hypercalcemia [4, 6, 10].

The contribution of vitamin D and its analogues to the occurrence of immune-mediated events have been studied; for example, adequate exposure in the antenatal and perinatal period and in the first few months of life are associated with less atopy in later life [11]. The role of vitamin D outside of calcium and bone regulation is also becoming better understood. Receptor-bound vitamin D plays a role in the expression of genes regulating immune responses and skin and gut barrier integrity [12]. An inverse relationship between vitamin D levels and immune response is well documented, but questions persist about the potential for allergic reactions, especially when supratherapeutic doses are used [13].

While vitamin D toxicity and deficiency are well understood, allergic reactions to supplemental forms of oral vitamin D are extremely rare. Three other cases have been reported in the literature [14–16]: two with type 1 hypersensitivity and one with delayed type 4 hypersensitivity. This case report presents a case of suspected mixed immediate and delayed allergy to an oral vitamin D supplement in a 53-year-old woman.

Case presentation

A 53-year-old Caucasian female with a history of asthma, Hashimoto's disease, depression/anxiety, idiopathic intracranial hypertension, irritable bowel syndrome (IBS) with fructan, lactose and glacto-oligosacchardie malabsorption, and acquired foraminal stenosis and radicular compression of the midcervical spine presented to her general practitioner (GP) for routine monitoring. Her allergy-specific history included immunoglobulin (Ig)-E-mediated allergies to crustaceans, bivalves, and selected fin fish. She also has contact urticaria with specific plants. Medications in use at the time of initial presentation to the GP were levothyroxine, citalopram, and topiramate. Her asthma was mild and intermittent, with no requirement for inhaled corticosteroid for more than 10 years, and only very occasional need for inhaled salbutamol for acute respiratory symptoms. Her family history included her mother, with photosensitive urticaria and primary sclerosing cholangitis, and her 20-year-old son, who had IBS and unspecified (and as-then unreported) adverse reactions to vitamin D.

Her serum 25(OH)D level was low (48 nmol/l; reference range 50–100 nmol/l). Owing to her age and perimenopausal status, she was prescribed 1000 IU cholecalciferol daily. Other pathology results were unremarkable (Table 1). She re-presented to the GP after 14 days, complaining of dyspepsia and stomach cramps within 20 min of taking the supplement. An alternative formulation of cholecalciferol was recommended (Ostevit-D; Key Pharmaceuticals Pty Ltd, Macquarie Park, New South Wales, Australia) at a dose of 14,000 IU Vitamin D3 (350 mcg colecalciferol) once a week, and monitoring was continued. Excipients in this product are listed in Table 3.

However, 2 days later, she developed a pruritic, fine vesicular rash specifically between her mid-trunk and knees, which lasted 3 days. Her asthma also significantly flared, and then 3 weeks later, she presented again with a fine, vesicular, non-itchy generalized rash. She also developed angular stomatitis and gut symptoms (nausea, pain, or loose stools) following high vitamin-D-containing foods, including the following:

- Margarine (fortified with vitamin D),
- Rye, malted barley, and yeasts (e.g., in bread premix),

Table 1 Pathology results

	Reference range	28/10/2022	19/01/2023
Sodium (mmol/l)	135–145	139	145
Potassium (mmol/l)	3.5–5.5	4.2	4.0
Chloride (mmol/l)	95–110	107	107
Urea (mmol/l)	3.0–8.0	5.5	5.1
Creatinine (umbel/l)	45–85	77	79
eGFR (ml/min/1.73m^2)	> 89	77	74
Bicarbonate (mmol/l)	20–32	25	26
Total bilirubin (mmol/l)	3–15	5	8
ALP (U/l)	30–115	54	48
25(OH)D (nmol/l)	> 49	48	51
Hemoglobin (g/l)	115–165	133	137
HCT	0.36–0.47	0.42	0.42
MCV (fl)	80–100	94	92
WCC (/nl)	4.0–11.0	4.0	3.5
Neutrophils (/nl)	2.0–7.5	1.7	1.8
Lymphocytes (/nl)	1.0–4.0	1.8	1.3
Monocytes (nl)	0.2–1.0	0.3	0.3
Eosinophils (/nl)	< 0.5	0.2	0.11
Basophils (/nl)	< 0.3	< 0.1	0.04
Platelets (/nl)	150–400	216	195
Lipase (U/l)	< 70	–	34
Total IgE (kIU/l)	0–100	–	145
Allergen specific IgE		–	0.35kU/l (negative)
ENA antibody screen		–	Negative
SS-A (Ro-60) antibody		–	Negative
Ro-52 antibody		–	Negative
SS-B antibody		–	Negative
Sm antibody		–	Negative
RNP antibody		–	Negative
Scl-70 antibody		–	Negative
PM-Scl 100 antibody		–	Negative
Jo-1 antibody		–	Negative
CENP B antibody		–	Negative
P-ANCA (IFA)		–	Indeterminate
MPO-ANCA (Luminex)		–	Negative
PR3-ANCA (Luminex)		–	Negative
Antinuclear antibodies		–	Negative

- Egg, especially egg yolks,
- Swordfish, salmon, tuna, mackerel,
- Mushrooms,
- Dairy, especially ricotta cheese,
- Pork and some delicatessen meats,
- Almonds.

Further testing was ordered. An abdominal ultrasound was requested, and the patient was referred to an allergy clinic for further investigation and management. The first appointment at the allergy clinic was 71 days after referral. Avoidance of the foods listed above was helpful but not curative.

The ultrasound and pathology results (Table 1) were unremarkable except for elevated total IgE levels (total IgE 145 kIU/l; reference range 0–100 kIU/l) and borderline 25(OH)D levels (51 nmol/l). Serum-specific IgE to staple food mix (including soy) was negative. Skin prick tests at the allergy clinic, using Inmunotek extracts for food, were as follows: crab 2 mm, king prawn 4 mm, salmon 0 mm, Trevalla 0 mm, pink ling 0 mm, tuna 0 mm, mussel 1 mm, scallop 3 mm, oyster 3 mm, octopus 0 mm, soy 0 mm, coconut 0 mm, and Osteovit D 7000 IU capsule liquid from caplet 0 mm. Patch testing for OsteovitD 7000 IU was negative after days 3 and 5. Her bone mineral densitometry results revealed normal bone mineral density in the lumbar spine, left hip, and left femoral neck.

A diagnosis of vitamin D hypersensitivity, with clinical features of a mixed IgE-mediated (Type 1) and non-IgE-mediated (Type 4) mechanism. Oral antihistamines (cetirizine 10 mg, as needed) were prescribed and proved effective. Her prescribed vitamin D supplementation was ceased and she was advised to avoid foods rich in vitamin D and obtain sufficient exposure to sunlight.

An oral vitamin D desensitization program was commenced using a modified protocol as described by Anantharajah et al. [15] Day 1 of the protocol was conducted in a community-based allergy clinic. Baseline lung function tests (normal), fractional nitrous oxide (11 ppb), and peak expiratory flow rates (480 l/min) were performed before starting with 1 IU compounded cholecalciferol[1] (using a 10 IU/ml then 1000 IU/ml solution in MCT[2] oil) manufactured by a local compounding pharmacy. Observations were recorded every 15 min.

During the ultra-rush up-dosing phase, the patient tolerated 1 IU, and then 2 IU was given 1 h later. When

[1] Vitamin D3 liquid 1 million IU/g (PCCA Australia, Matraville, New South Wales, Australia).

[2] *MCT* medium chain triglycerides; MCT Oil (Nutricia, Chatswood, New South Wales, Australia).

given 4 IU after a further hour, she reacted with lip irritation and burning and then feeling generally unwell and nauseous. This settled with oral antihistamines (cetirizine 20 mg) over the following 30 min. The ultra-rush build-up was stopped at the 3 h mark. Her peak expiratory flow rates did not decrease, and her oxygen saturation and other vital signs remained normal. A much slower up-dosing of 2 IU daily was used in week 2, after which it doubled for most weeks (Table 2). Daily cetirizine (10 mg) was taken as a preventative measure. Each up-dose was conducted at an allergy clinic with a 1-h observation period. Subsequent daily doses were administered at home.

There were some occasional reactions during the build-up phase: after the dose reached 4 IU (day 8), the patient described lip itching, and 4 h later, reported chest tightness but no wheeze. There was delayed abdominal pain 2 days later. At the end of week 3, the patient reported no oral symptoms but was experiencing "brain fog," chest tightness (which improved immediately with inhaled budesonide/formoterol), and delayed abdominal discomfort. This prompted a pause in up-dosing. At the start of week 7, approximately 1 h after taking vitamin D, she developed nausea followed by right-sided headache, particularly over and above the right eye. These symptoms mostly resolved within 15 min of a single dose of antihistamine, and no additional doses of antihistamines were required over the next 24 h. The build-up dose was titrated back to 40 IU. No further adverse effects were reported. Overall, the 18-week desensitization program was well tolerated with no further alteration of the up-dosing protocol required.

At the 6-month follow-up, the patient was able to tolerate the commercial preparation of vitamin D to which she had previously reacted. Her current maintenance dose is 1000 IU cholecalciferol (Ostelin; Sanofi Consumer Healthcare, Virginia, Queensland, Australia) daily, and this was recommended to be taken indefinitely to ensure ongoing tolerance to vitamin D, as well as to reduce the risk of morbidity (such as osteoporosis) due to vitamin D deficiency. Her asthma was quiescent, and there were no further skin or gut symptoms. She continued on 10 mg cetirizine daily, mostly due to patient choice, as she felt this would likely prevent immediate oral, gut, or lung symptoms. Sustained unresponsiveness to cholecalciferol supplements after a period of prolonged abstinence (>6 weeks) was not checked in our patient, as she preferred to continue with a maintenance dose for bone health reasons.

Gradual reintroduction of vitamin D-rich foods, such as salmon and ricotta, caused a significant recurrence of gut symptoms. Foods with low vitamin D content have been reintroduced slowly with no flare of gastrointestinal symptoms. The patient's GP continues to provide ongoing monitoring and routine primary care.

Figure 1 presents a timeline of events for this case.

Table 2 Cholecalciferol immunotherapy schedule

Step	Oral dose (IU)	Dilution (IU/ml)	Volume (ml)
Administered in allergy clinic			
Time/week			
0 h	1	10	0.10
1 h	2	10	0.20
2 h	4	10	0.40
Administered at home			
Week 1	2	10	0.20
Week 2	4	10	0.40
Week 3	8	10	0.80
Week 4	8	10	0.80
Week 5	16	10	1.60
Week 6	32	10	3.20
Week 7	64	10	6.40
Week 8	40	1000	0.04
Week 9	60	1000	0.06
Week 11	120	1000	0.12
Week 13	240	1000	0.24
Week 15	500	1000	0.50
Week 17	750	1000	0.75
Week 18	1000	1000	1.00

Discussion

This case report highlights a likely allergic reaction to supplemental vitamin D. Aside from hypercalcemia associated with vitamin D excess, few studies have described allergic adverse reactions to vitamin D [14–16]. Amandeep et al. [14] provided the first published case of a vitamin D allergy presenting as a pruritic rash, though consistent with a delayed hypersensitivity (T-cell mediated) reaction. Unal et al. [16] and Anantharajah et al. [15] both described cases presenting with rash, with synovitis present in the latter. The case presented here had symptoms strongly suggestive of both immediate and delayed mechanisms.

Hyppönen et al. [13] commented on the role of vitamin D in causing IgE-mediated hypersensitivity and suggested a nonlinear relationship between 25(OH)D and IgE levels. This may suggest a threshold above (and below) which hypersensitivity is more common. Alswailmi et al. [17] also reported that supratherapeutic levels of vitamin D were associated with IgE hypersensitivity in adult patients with preexisting atopic conditions. Other studies also suggest that high doses of vitamin D are not without risk [18, 19].

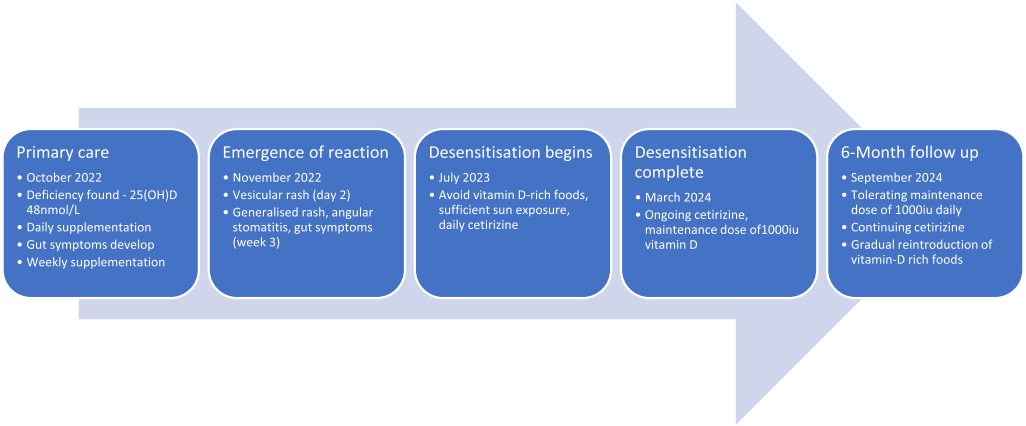

Fig. 1 Timeline of event

Although the patient in this case was never known to have supratherapeutic levels of 25(OH)D, this does not exclude the likelihood of an immune-mediated response to the supplement. She has a history of atopy (i.e., asthma), thus she may have been more sensitive to large doses of vitamin D. A lack of acute asthma, allergic symptoms, or intolerance prior to using supplements is highly suspicious of a drug reaction [20].

To confirm the causative antigen in allergic reactions, it is best to perform a confirmatory test. In this case, skin prick and patch tests were negative. Interestingly, there were also no confirmatory positive tests in any of the other reported cases of hypersensitivity to vitamin D in the literature [14–16]. It is well known that skin prick tests that screen for immediate IgE drug reactions have low sensitivity [21]. For delayed type reactions, patch testing and delayed intradermal testing can have high specificity if positive. Clinical history remains very useful in determining likely drug reactions. Ultimately, a provocation test with the suspected allergen is the gold standard test although it does carry risks.

In the absence of a reliable test to determine whether there was cholecalciferol hypersensitivity, we used the Naranjo scoring system [20] to estimate the probability of a drug reaction. A Naranjaro score of 5–8 suggests a probable drug reaction [20]. Our patient's probability of having a cholecalciferol allergy was classified as "probable" (score of 7) on the basis of temporal factors (+2 in Naranjaro score), reappearance of symptoms with readmission (+2), no other likely precipitants (+2), and clinical improvement with drug withdrawal (+1).

In this case, the patient's symptoms suggested a type 4 (delayed) hypersensitivity. Type 4 hypersensitivity is characterized by an exaggerated, often persistent, delayed response to environmental antigens, and subsequent T-cell activation. The persistent symptom in this case included a delayed rash, nausea, dyspepsia, loose bowel motions, and increased pain [22].

However, there were also symptoms more typically seen with an immediate (Type 1) hypersensitivity. This type of response is mediated by IgE antibodies and mast cells in response to allergens, and typically causes increased permeability of the vasculature and mucosal secretions, and eventually inflammation [22] and systemic symptoms [23]. Some "soft" early onset symptoms of IgE-mediated hypersensitivity (e.g., lip itching, abdominal pain, nausea, chest tightness) were evident in this case, but more definitive symptoms (e.g., urticaria, angioedema, objective respiratory distress, or cardiovascular compromise) were absent. The emergence of asthma symptoms, relieved by inhaled beta$_2$ agonists medication, during the up-dosing phase of the desensitization when previously the patient's asthma was tightly controlled [22], as well as the blocking of future immediate reactions with antihistamines during up-dosing, does give some support to a partial IgE-mediated mechanism.

Although there is a highly suspicious temporal association with the use of the supplement here, many other potential precipitants of the reaction must be considered. Excipients in the supplement preparation may have been responsible, although the inactive ingredients are not dissimilar to those found in other therapeutic products [24] (Table 3).

Table 3 Excipients contained in the OsteVit-D One-A-Week cholecalciferol 7000 IU (175 mcg) capsule

Butan-1-ol	Glycerol	Shellac
Dl-alpha-tocopherol	Iron oxide black	Soya oil
Ethanol	Isopropyl alcohol	Strong ammonia solution
Fractionated coconut oil	Propylene glycol	Sulfuric acid
Gelatine	Purified water	Vegetable oil

While this patient was advised to obtain vitamin D via exposure to sunlight, it is common for Australians from the southeastern states to be vitamin D deficient [2]. Achieving adequate 25(OH)D levels through sun exposure alone can be difficult to achieve, especially at lower latitudes. Approximately 30 min of sun exposure during winter is required for residents of southern Australian state capitals to maintain adequate levels of vitamin D [5].

Desensitization in patients who are allergic, and where the ongoing use of supplemental vitamin D is the only means of maintaining adequate blood levels, is achievable and has been previously documented [14–16]. Effective medication desensitization, including supplements, in type 1 and 4 hypersensitivity appears to be relatively low risk with tailored dosing regimens and careful monitoring [25]. To ensure desensitization to the active drug (here cholecalciferol) rather than excipients, it is recommended to use the compounded pure drug in edible oil, as in Anatharajah et al.'s [15] study. Indefinite maintenance doses of the drug are required to ensure ongoing tolerance as prolonged abstinence can precipitate a resumption of the allergic state to that drug and the need for further up-dosing.

Conclusion

Vitamin D deficiency is frequently and easily detected in primary care, and oral supplementation is usually sufficient to reduce the risk of subsequent morbidity. Intolerance to vitamin D supplementation, as with any medication, can be caused by allergic mechanisms. When oral vitamin D supplementation to prevent acute and long-term health problems is unavoidable, desensitization is a practical option. Vitamin D desensitization using personalized, flexible dosing with careful monitoring during up-dosing and long term maintenance under the care of a multidisciplinary team of primary care physician, pharmacist, and allergist can lead to an effective outcome.

Abbreviations

25(OH)D	25-Hydroxyvitamin D
GP	General practitioner
IBS	Irritable bowel syndrome
IU	International units

Acknowledgements

The authors wish to thank the patient for her cooperation as this manuscript was prepared.

Author contributions

AR: data collation, draft manuscript, review and editing, documentation; NC: clinical care, draft manuscript, review and editing; and BS: clinical care, conceptualization, review and editing. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

An exemption from ethical review was granted by the University of Tasmania Human Research Ethics Committee (Project ID: 30944).

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that there are no conflicts of interest.

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Received: 1 August 2024 Accepted: 15 January 2025
Published online: 15 July 2025

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