Case report

Omenn syndrome in a 10-month-old male with athymia and VACTERL association

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We describe the case of a 10-month-old boy with vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association and athymia who developed Omenn syndrome. (J Allergy Clin Immunol Global 2023;2:100153.)

Key words: *Athymia, cultured thymic epithelial transplantation, DiGeorge syndrome, 22q11.2 deletion syndrome, Omenn syndrome, T-cell receptor rearrangement excision circle, VACTERL association*

Abbreviations used
DGS: DiGeorge syndrome
OS: Omenn syndrome
SCID: Severe combined immunodeficiency
VACTERL: Vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities

Congenital athymia is a condition defined by the absence of a functional thymus gland. Athymia has been described as a feature in various genetic disorders such as the following: DiGeorge syndrome (DGS) due to heterozygous *22q11.2* deletion and/or *TBX1* mutation; coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary abnormalities, and ear abnormalities (CHARGE) syndrome due to *CHD7* mutation; *FOXN1* deficiency (nude/severe combined immunodeficiency [SCID]) due to *FOXN1* mutation; and otofaciocervical syndrome type 2 due to *PAX1* mutation. Recently, case reports of *TBX2* and *FOX13* mutations have been implicated as causing athymia.[1] In addition, diabetic embryopathy and *in utero* exposure to retinoic acid have been linked to altered fetal thymus size.[2] Athymia has also been reported in vertebral defects, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb (radial) anomalies (VACTERL) association, which describes a clustering of congenital malformations.[3] Currently, there is no evidence indicating a single unifying cause of VACTERL association, and as such it is considered an association rather than a syndrome. There are no strict diagnostic criteria; however, it is accepted that the presence of 3 component features is required for diagnosis. There are case reports highlighting an overlap between VACTERL association and *22q11* deletions and duplications.[3] Nguyen et al[4] described a patient with *22q11* microduplication and features of VACTERL association. The patient discussed in this article was reported to have vertebral deformity, a vascular ring, tracheoesophageal fistula with esophageal atresia, cardiac malformations (ventricular septal defect and double aortic arch), and limb abnormalities.[4] This was the second such known case of VACTERL association and a *22q11* microduplication.[4] In this report, we present a patient with VACTERL association and athymia/DGS who developed Omenn syndrome (OS).

CASE REPORT

The patient was a full-term male born via cesarean section with features of VACTERL association identified during prenatal care. These features included multiple vertebral abnormalities, tetralogy of Fallot with hypoplastic pulmonary valve, and unilateral renal agenesis. The patient was macrocephalic without hydrocephalus. At birth, he required mechanical ventilation for respiratory distress due to significant chest wall deformity (Fig 1, *A*). He also had hypocalcemia and hypoparathyroidism. The patient received parenteral and enteral calcium supplementation and required pulmonary valvuloplasty and patent ductus arteriosus stenting by the cardiology department.

The immunology department was consulted following an abnormal result of newborn screening for SCID. The cycle threshold of the T-cell receptor rearrangement excision circle was 45 (abnormal ≥ 40) performed at when the patient was 1 day old and repeated at age 7 days. A flow cytometry study at age 2 weeks revealed absent $CD3^+$ T cells (13 cells/mm^3) and $CD4^+CD45RA^+$ naive T cells (13 cells/mm^3) but normal $CD19^+$ B-cell levels (588 cells/mm^3) and $CD56^+$ natural killer cell levels (175 cells/mm^3) (Table I). The patient's serum IgG level was normal. Chest radiography revealed marked chest wall deformities (Fig 1, *A*) and absent thymic shadow (Fig 1, *B*). Of note, there was gestational diabetes in the mother, which was treated with insulin starting at 21 weeks' gestation; however, no other conditions or medication use that have been associated with DGS were reported. There was no known parental consanguinity. Repeat studies at when the patient was 2.5 monthsold revealed a similar finding of absent $CD3^+$ T cells (0 cells/mm^3) and

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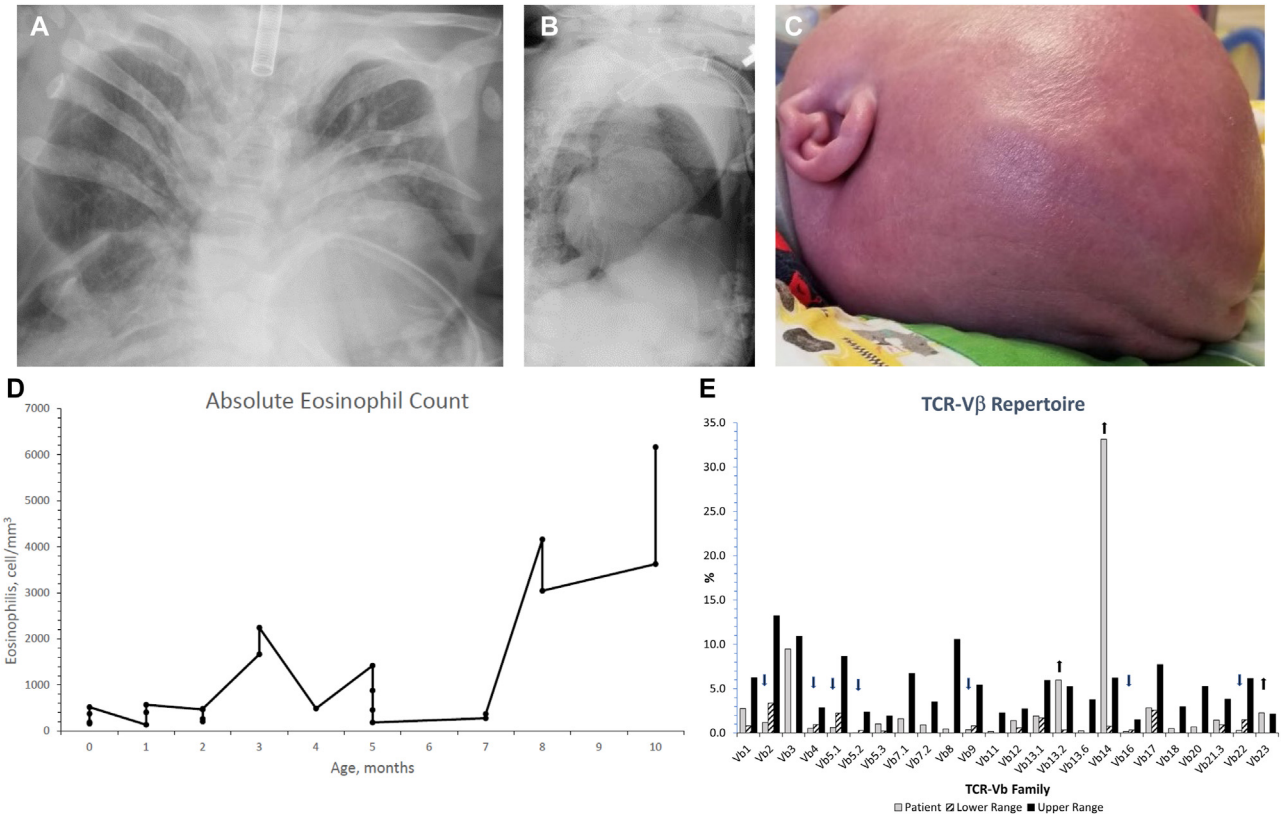

FIG 1. Chest wall deformity (**A**) and absent thymus (**B**) in a newborn boy with VACTERL association. At age 10 months, the patient developed a diffuse scaly erythrodermic skin rash and alopecia, as shown on the scalp (written parental consent for use of the photo has been obtained) (**C**), and he developed eosinophilia (**D**) associated with generalized lymphadenopathy and splenomegaly consistent with OS. TCR-Vβ families study by flow cytometry (**E**) (Cincinnati Immunology Laboratory) demonstrated oligoclonal T cells with increased (↑) TCR-Vβ 13.2, Vb14, and Vb23 and decreased (↓) TCR-Vβ2, Vb4, Vb5.1, Vb5.2, Vb9, Vb16, and Vb22.

TABLE I. Immunologic studies in a 10-month-old infant boy with VACTERL association and athymia who developed OS

Indicator	Patient at age: 0.5 mo	2.5 mo	10 mo	Normal range at age 6-12 mo
Date of testing	February 24, 2020	April 23, 2020	December 18, 2020	
IgG level (mg/dL)	531	608	768	363-971
IgA level (mg/dL)		<5	152	12-73
IgM level (mg/dL)		33	18	43-174
IgE level (IU/mL)			5096	3-15
AEC (cells/mm^3)	375	266	6116	0-400
ALC (cells/mm^3)	1250	2926	1807	3400-9000
CD3$^+$ cells (cells/mm^3), no. (%)	25 (2%)	0 (0%)	705 (39%)	1900-5900 (49-76)
CD4$^+$ cells (cells/mm^3), no. (%)	13 (1%)	29 (1%)	181 (10%)	1400-4300 (31-56)
CD8$^+$ cells (cells/mm^3), no. (%)	0 (0%)	0 (0%)	434 (24%)	500-1700 (12-24)
CD19$^+$ cells (cells/mm^3), no. (%)	588 (47%)	1434 (49%)	813 (45%)	610-2600 (14-37)
CD56$^+$ cells (cells/mm^3), no. (%)	175 (14%)	878 (30%)	108 (6%)	160-950 (3-15)
CD4$^+$CD45RA$^+$ cells (cells/mm^3), no. (%)	13 (100%)	25 (86%)	2 (1%)	1100-3700 (64-93)
CD4$^+$CD45RO$^+$ cells (cells/mm^3), no. (%)	0 (0%)	4 (14%)	172 (95%)	160-800 (5-18)

AEC, Absolute eosinophil count; *ALC*, absolute lymphocyte count.

CD4$^+$CD45RA$^+$ naive T cells (25 cells/mm^3) (Table I). The result of whole genome chromosome single-nucleotide polymorphism microarray analysis was normal, and the result of testing with a primary immunodeficiency 407 gene panel that included *TBX1, CHD7,* and *FOXN1* (Invitae) was normal. The genetics department did not recommend that whole exome sequencing be performed initially owing to the lack of known genes associated with VACTERL association. Also, a hematopoietic stem cell–autonomous defect was not ruled out, as the patient's CD34$^+$ cells were not cultured in an artificial thymic organoid

system. A diagnosis of complete DGS superimposed on VACTERL association was made, and the patient was treated conservatively with subcutaneous immunoglobulin and prophylactic sulfamethoxazole and trimethoprim. Because of the chest wall deformity requiring respiratory ventilation, the patient was deemed unsuitable for transfer to Duke Medical Center to receive a cultured thymic epithelium transplant. Additionally, the patient could not be transferred for chest wall repair until cultured thymic epithelium transplantation had been performed. He continued to receive immune globulin replacement and prophylactic antibiotics until age 8 months. He experienced interval infections up until that point; these infections included recurrent pneumonias that were successfully treated with antibiotics. The patient had no history of viral or fungal infections.

Subsequently, the immunology department was consulted again when the patient was 10 months-old to evaluate the development of generalized lymphadenopathy, splenomegaly, generalized eczematous skin rash, and eosinophilia that began at age 8 months. The eczema was characterized as a scaly erythrodermic rash of the entire body and generalized alopecia (Fig 1, *C*). As seen in Fig 1, *D*, the patient's blood eosinophil count increased dramatically at age 8 months, peaking at 6116 eosinophils/mm^3 at age 10 months. His serum IgE level was also dramatically increased at age 10 months (5096 IU/mL). Further immunologic evaluation revealed levels of $CD3^+$ T cells (705 cells/mm^3) and $CD4^+CD45RO^+$ memory T cells (172 cells/mm^3) that were increased from the levels found in previous studies (Table I). Examination of TCR-Vβ families by flow cytometry (Cincinnati Immunology Laboratory, Cincinnati, Ohio) demonstrated oligoclonal T cells. The result of examination for maternal engraftment was negative, with 100% XY as determined by fluorescence *in situ* hybridization (Mayo Clinic Laboratory, Rochester, Minn). A diagnosis of OS in our patient with VACTERL association and now atypical complete DGS was established. His OS was initially treated with methylprednisone, 2 mg/kg per day. The patient improvement markedly, with resolution of the rash, splenomegaly, and lymphadenopathy, and methylprednisolone was gradually tapered. However, there was a recurrence of the patient's erythroderma after tapering of the steroids. He subsequently continued receiving prednisone (2 mg/kg per day) throughout most of his hospital stay. Whole exome sequencing (GeneDx, Gaithersburg, Md) was performed; it showed biparental inheritance of 2 *WNT10A* variants, a paternally inherited pathogenic mutation (*c.682T>A; p.F228I*), and maternally inherited variant of uncertain significance (VUS) (*c.649G>A; p.D217N*). *WNT10A* mutations, even in a heterozygous form, can be associated with ectodermal dysplasia–associated conditions, including dry skin, dystrophic nails, oligodontia, and sparse hair. The parents did not have any clinical evidence of ectodermal dysplasia other than early-onset alopecia in the father and eczema in a sibling.

DISCUSSION

This case highlights a rare presentation of VACTERL association with initial lymphopenia as a result of a clinical diagnosis of complete DGS and subsequent development of OS. Congenital athymia leads to profound T-cell immunodeficiency with absent T cells but normal B-cell and natural killer cell levels. The immunodeficiency of VACTERL association with athymia needs to be differentiated from other congenital immunodeficiencies, such as SCID and/or combined immunodeficiency. Patients with DGS and VACTERL association have increased susceptibility to infections, development of graft-versus-host disease, and now OS. For athymia, cultured thymus epithelial tissue implantation is the preferred treatment in addition to antimicrobial prophylaxis and immunoglobulin replacement.[5] Without thymus transplantation, athymia is fatal, with almost all children dying from infections by age 2 years. Comorbidities associated with underlying disorders can also interfere with ability to receive a thymic transplant, as was the case for this patient.[6] Hematopoietic stem cell transplantation has been performed in patients with congenital athymia. However, survival after hematopoietic stem cell transplantation in patients with congenital athymia is low compared with that in patients with SCID (41% versus ≤90%, respectively).[2]

Our patient developed OS at age 8 months. OS is a distinct inflammatory process that can be associated with genetically diverse SCID disorders. As opposed to typical patients with SCID, who have a paucity of lymphoid tissue, patients with OS have enlarged lymph nodes and splenomegaly. They also develop generalized erythroderma, as well as alopecia and loss of eyebrows and eyelashes. Other presenting symptoms include chronic diarrhea, pneumonitis, and failure to thrive during the first year of life.[5] Eosinophilia and elevated IgE level are frequently present. OS is caused by oligoclonal expansion of autoreactive T cells as a result of abnormal thymic negative selection. In addition, there is an absence of proper regulation by other immune system components, such as IL-10 and regulatory T cells. OS may be associated with various syndromic disorders, including SCID, cartilage hair hypoplasia, DGS, and coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary abnormalities, and ear abnormalities (CHARGE) syndrome. These associated disorders must be considered when encountering a patient with OS.[5]

Previous case reports have described an overlap between VACTERL association and *22q11* deletions and/or duplications as well as OS with atypical complete DGS.[4,7] Stone et al[7] reported a case of an infant with atypical complete DGS and OS. The patient presented with erythroderma, unilateral kidney agenesis, tetralogy of Fallot, pulmonary atresia, ventricular septal defect, and absent thymus. Laboratory findings included eosinophilia, elevated IgE level, undetectable T-cell receptor rearrangement excision circle, oligoclonal T-cell population, and abnormal TCR-Vβ spectratyping. The patient's genetic testing results were negative, with no *22q11* deletion. It is notable that *22q11* deletions are not the only pathway by which atypical DGS can occur.[7] Oligoclonal T-cell expansion in the setting of complete DGA is considered an atypical phenotype. The increased number of T cells develop at some point after birth, and maternal engraftment must be ruled out before making the diagnosis. Markert et al[8] estimated that approximately 30% of patients with DGA have an atypical DGA or OS-like phenotype. Although there are previous reports of overlap between features of VACTERL and DGS with *22q11* deletions, as well as OS and DGS, to our knowledge, a patient with overlapping features of VACTERL association with athymia and OS without *22q11* deletion has not been reported.

Many of aforementioned conditions that overlap with OS and athymia also have clinical overlap and multiple features in common with VACTERL association and thus should be considered in the differential diagnoses. VACTERL association is estimated to be present in between 1 to 10,000 and 1 to 40,000 live births, such that on the basis of the current literature, this

combination of VACTERL association with atypical complete DGS remains very rare. The etiology of VACTERL association remains unknown. The condition is typically sporadic and often has many comorbid conditions. There is likely causal and clinical heterogeneity.[2] Adam et al[9] recently reported an overlap between VACTERL association and a number of other multiple embryonic malformations, and they have termed this group of conditions *recurrent constellations of embryonic malformations*, the etiologies of which are currently unknown. Further research into the potential association and molecular etiologies of VACTERL association and athymia with OS is needed.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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