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A Case of Atypical, Complete DiGeorge Syndrome without 22q11 Mutation

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Keywords

atypical; complete DiGeorge syndrome; Omenn syndrome; erythroderma; eosinophilia; T cell deficiency

A four month old male infant presented in consult to allergy and immunology with eosinophilia, (3 separate counts greater than 3000/mm³) and an erythrodermic rash. The infant had known unilateral kidney agenesis, tetralogy of Fallot, pulmonary atresia and ventriculoseptal defect. He had undergone an initial cardiac repair with a Blalock-Taussig shunt at 19 days of life. The patient received one transfusion, with irradiated packed red blood cells, at one month of age. At age two months the infant had been admitted to the intensive care unit (ICU) for hypotension presumed secondary to sepsis from an unclear source. He was treated with vancomycin and cefepime until the presence of respiratory syncytial virus was detected. At age three months, necrotizing enterocolitis was suspected due to hemodynamic instability and blood flecked stools. He was treated empirically with vancomycin and piperacillin-tazobactam. One week after completing treatment, he was noted to have increasing transaminases, splenomegaly, eosinophilia, and rash, at which point a drug related rash was suspected.

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The physical examination at four months revealed an irritable child with normal facies save for low-set, posteriorly-rotated ears with a slight notch, erythroderma, (Figure 1), easily plucked hair, hepatomegaly, splenomegaly, and cardiac murmur. Chart review revealed absolute lymphopenia with the absolute lymphocyte count (ALC) ranging from 500 to 650/mm³ consistently during the first two months of life, rising to a normal ALC at 4 months of 4550/mm³ (Table 1 contains repeated lab values). Absolute eosinophil counts gradually trended from 500/mm³ at 2 months of age to 4000/mm³ at 4 months. Transaminases were elevated, with an aspartate aminotransferase (AST) of 350 U/L and an alanine aminotransferase (ALT) of 700 U/L. Review of operative notes and chest x-rays suggested an absent thymus. Fluorescence *in situ* hybridization for a 22q11.2 deletion was normal, though chromosomal microarray revealed several large regions of homozygosity encompassing >2.4% of the child's genome suggesting the parents were related as second cousins. Family history was negative for increased infections or early childhood deaths. The mother had uncontrolled diabetes mellitus during pregnancy and a history of lymph node abscess. The father's history was not available.

Skin biopsy performed at 4 months for Langerhans cell histiocytosis showed acanthosis, spongiotic epidermal changes, and sarcoidal-appearing granulomas without any signs of Langerhans cells. CD3 staining was performed showing that the majority of the lymphocytes present in the granulomas were T cells. Bone marrow biopsy to test for myelodysplastic hypereosinophilic syndrome diagnosis was done at 4 months of age, showing 4% B cells, 16% T cells, no increase in blasts by CD33, CD34, CD45 or on forward scatter/side scatter gating and normal platelet derived growth factor gene mutation analysis. The clinical history was not consistent with drug rash given the length of time from possible offending agents, and as the patient's eosinophilia had been present prior to the initiation of antibiotics. As time went on, the infant's rash and eosinophilia continued despite avoidance of antibiotics that he had previously received. Strongyloides titers were negative.

An immunologic workup at 4 months revealed normal baseline IgM 87 mg/dl (ref 20-90), IgA 19 mg/dl (ref 8-91), IgG 308 mg/dl (ref 110-700), but an elevated IgE of 1664 IU/ml (ref 0-30). Tetanus and pneumococcal IgG titers were nonprotective; the patient was as yet unvaccinated. Flow cytometry revealed elevated total CD3+ cell count of 3640 (ref 1700-3600), but normal CD3+/CD4+ cell counts of 2639 (ref 1000-2800), CD3+/CD8+ cell counts of 1001 (ref 800-1500) and CD19+ cell counts of 728 (ref 500-1500). There was mild diminishment in absolute CD 56+/CD16+ cell counts at 136/mm³, ref (200-700), though counts were normal subsequently. Lymphocyte proliferation assays were low to phytohemagglutinin, pokeweed and concanavalin A. T cell receptor rearrangement excision circle copies were undetectable despite normal absolute CD3+, CD4+, and CD8+ cells counts. T-cell Receptor Variable Region Beta (TCR V β) spectratyping revealed oligoclonal T cell populations (Online Figure). T-cell phenotyping revealed a complete absence of naïve T-cells and the T cells that were present were of an activated phenotype (Table 1). Studies of recent thymic emigrants revealed absent recent thymic emigrants despite an elevated total absolute CD4 count of 3291/mm³ (ref 153-1745), suggesting no thymic output. Subsequent maternal engraftment studies showed the absence of maternal XX karyotype in whole blood sample of the male infant.

The differential diagnosis narrowed to a leaky version of SCID/Omenn's syndrome versus atypical complete DiGeorge syndrome, with oligoclonal T cells. Subsequent genetic testing for *RAG1*, *RAG2*, *ARTEMIS*, *CD3D*, *CD3E*, *CD3Z*, *IL2RG*, *IL7R*, *JAK3*, *PNP*, *PTPRC*, *RMRP*, and *ZAP70* gene mutations was negative. The results suggest that the patient has thymic aplasia and an atypical, complete DiGeorge syndrome with autoreactive T cells, though autoreactivity was not confirmed. Subsequent *TBX1* gene sequence analysis and *CHD7* gene sequence analysis to search for known DiGeorge or CHARGE syndrome variants also returned negative. Data have shown that only half of patients with complete DiGeorge have 22q11.2 deletion syndrome.¹ Whole exome sequencing was not obtainable due to financial constraints.

The patient was initially treated at age 6 months with cyclosporine, intravenous methylprednisolone 2mg/kg for three days, topical emollients, and immune globulin replacement. His rash and organ dysfunction improved significantly within days of therapy initiation and at age 7 months he was able to receive full repair of his cardiac condition. His rash improved further with addition of daily fluocinolone oil and pimecrolimus creams. Subsequently he was stable for discharge at age 9 months on oral cyclosporine and infusions of IVTG. The patient was noted to have rhinovirus and parainfluenza virus 3 infection on routine testing of a nasopharyngeal aspirate at 12 months of age. He developed acute varicella infection at 13 months of life with rash and a varicella zoster virus (VZV) copy number of 11,400 copies/ml. He was treated with IV acyclovir for 3 weeks and then was changed to valacyclovir. At 14 months of age he underwent laparoscopic esophagogastric fundoplasty. One week later, the VZV copy number rose to 900 and then 5500 copies/mL. He developed an oxygen requirement and enlarged skin lesions. He was put back on IV acyclovir and the VZV copy number dropped to 1000/mL. He was given a cultured allogeneic thymus transplant at 14.75 months of age with pretransplantation rabbit anti thymocyte globulin and cyclosporine therapy. Unexpectedly, he could not be extubated until 3 days after the transplant surgery. He did fairly well until 17 days after surgery when he required initiation of high flow oxygen; he was reintubated 21 days after transplantation. He required the oscillator and high oxygen concentrations, had worsening renal function, and did not respond to diuretic therapy. He succumbed to respiratory failure on day 25 after thymus transplantation presumably due to parainfluenza virus 3, as 5 days prior to death his VZV copy number was <278/mL and parainfluenza virus 3 was still present in his secretions.

This patient met the criteria for complete DiGeorge Syndrome based on the absence of naïve T cells, plus congenital heart disease.^{2,3} Importantly, 22q11.2 deletion syndrome is not needed for the diagnosis of DiGeorge anomaly. Our patient is an infant of a diabetic mother.^{4,5} Infants like this patient represent approximately 15% of infants receiving thymus transplants for complete DiGeorge anomaly.¹ Patients in this group often have single kidneys.^{4,6,7} This patient developed an Omenn syndrome phenotype with oligoclonal T cells and rash at 4 months of age.⁸ These findings are characteristic of atypical, complete DiGeorge syndrome.⁹ This case may be of benefit to those who are faced with the difficult challenge of evaluating persistent eosinophilia and erythroderma in infancy. It is important to realize that not all cases of severe T cell deficiency present with lymphopenia. Most important for the practicing physician to know from this case is that the final common

pathway for the immune dysfunction in DiGeorge syndrome is failure of normal thymus formation and the resulting inability to create normal mature T cells. Potentially, had newborn screening for SCID been performed on our patient, he would have been identified and treated rapidly, hopefully avoiding the multiple infections that led to his death. Newborn T-Cell Receptor Excision Circles (TREC) screening implementation is becoming standard practice across state screening programs in the United States, and is able to capture infants who are unable to perform T-cell receptor rearrangement successfully.¹⁰ This should result in early diagnosis of patients similar to ours. As TREC screening programs become the standard across the country, it will be crucial to remember that 22q11 mutations are not the only pathway by which atypical, complete DiGeorge syndrome can occur.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Patient's rash at 4 months of life. Noted alopecia, erythroderma and desquamation.

Trends in laboratory testing over time

Table 1

Variable	Reference Range (for age 4 months old) *	Birth	2 Months of Age	4 Months of Age - Diagnosis	1 Year Old: Pre-Thymus Transplantation (on cyclosporine)
Complete Blood Count					
Hemoglobin (gm/dl)	13.5-22.6	13.4		12.0	14.8
MCV (fL)	93-118	97		94	
RDW (%)	11.1-14.3	15.5		18.4	
Platelet Count ($\times 10^3/\mu\text{L}$)	140-300	275		362	306
MPV	10.2-12	9.3		9.9	
White Blood Cell Count ($\times 10^3/\mu\text{L}$)	4.0-14.6	10 (age-adjusted ref: 9.4-31.1)	14.1	21.0	9.6
Absolute Lymphocyte Count ($\times 10^3/\mu\text{L}$)	2.5-9.8	1.95 (age-adjusted ref: 2.8-9.6)	1.26	7.94	3.17
Absolute Neutrophil Count ($\times 10^3/\mu\text{L}$)	1.5-7.7	5.95 (age-adjusted ref: 5.9-19.9)	11.56	6.85	5.4
Absolute Monocyte Count ($\times 10^3/\mu\text{L}$)	0.2-1	1.94	0.82	1.47	
Absolute Basophil Count ($\times 10^3/\mu\text{L}$)	0.01-0.08	0.02	0.02	0.09	
Absolute Eosinophil Count ($\times 10^3/\mu\text{L}$)	0-0.5	0.08	0.43	4.58	2.00
Flow Cytometry *					
Total CD3+ cell count	2500-5600			3640	1137
CD4+ T cell count	1800-4000			2639	868
CD8+ T cell count	590-1600			1001	247
NK cell count	200-700			136	371 and 1375
B cell count	430-3000			728	1597
% of CD4+ cells that are CD45RA+ (as % CD4+ T cells)	Ref: Comparison made to pediatric reference range: 2-18y <50%			0	
% of CD4+ cells that are CD45R0+ (as % CD4+ T cells)	Ref: Comparison made to pediatric reference range: 2-18y >=15%			99	
% of CD4+/CD31+ cells that are CD45RA+ (as % CD4+ T cells)	Ref: Comparison made to pediatric reference range: 2-18y 19.4-60.9			0	

Variable	Reference Range (for age 4 months old)*	Birth	2 Months of Age	4 Months of Age - Diagnosis	1 Year Old: Pre-Thymus Transplantation (on cyclosporine)
% of CD4+/CD62L+ cells that are CD45RA+	Ref: Comparison made to pediatric reference range: 2-18y-15-71%			0	0.3
% of CD8+/CD62L+ cells that are CD45RA+	Ref: Comparison made to pediatric reference range: 2-18y 8-81%			8	0.2
Evaluation for maternal engraftment by karyotyping for XX				Negative	
Lymphocyte Proliferation Studies					
Phyto-hemagglutinin 1:20 Stimulated (Counts per minute)	Control: 531285			Patient: 86604 (16% of control)	
Concanavalin A 1:40 Stimulated (Counts per minute)	Control: 810363			Patient: 5134 (0.6% of control)	
Pokeweed Mitogen 1:40 Stimulated (Counts per minute)	Control: 385733			Patient: 3575 (0.9% of control)	
Liver/Renal Function Testing					8 Months Old (on cyclosporine)
AST (unit/L)	34-518	104 (age adjusted ref: 32-162)		350	380
ALT (unit/L)	20-67	21 (age adjusted ref: 5-33)		700	38
Alkaline phosphatase (unit/L)	134-518	122 (age adjusted ref: 90-273)		389	380
Gamma Glutamyl Transferase (units/mL)	8-127	97		238	82
Total Bilirubin (mg/dL)	0.2-0.7	8.6 (age-adjusted ref: 0.2-12)		0.6	0.4
Blood urea nitrogen (mg/dL)	3-23	8		25	42
Creatinine (mg/dL)	0.42-1.05	0.64		0.39	0.47
C-reactive protein (mg/L)	0.1-1.0	0.5		41.5	0.6

* Flow cytometry reference range for 4 month old from Braun E. *The Harriet Lane Handbook (Chapter 15)*. 20th ed. Philadelphia, PA: Elsevier Saunders; 2015.

All other laboratory reference ranges as per age-adjusted reference ranges at Vanderbilt University Medical Center.