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**Case report**

# Dermatological clues to the diagnosis of atypical complete DiGeorge syndrome

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## Abstract

Atypical complete DiGeorge syndrome (DGS) is an extremely rare congenital disease characterized by an eczematous dermatitis, lymphadenopathy, and an oligoclonal T-cell proliferation. Because its initial presentation may be confused with other types of eczematous dermatitis, diagnosis and treatment are usually delayed. We describe herein a case of an infant with atypical complete DGS to draw attention to the clinical and histopathological findings that lead us to the diagnosis.

**Key words: DiGeorge syndrome, atypical complete DiGeorge syndrome, eczematous eruption, neonatal rash**

## Case synopsis

A 3-month-old infant born at 37 weeks gestational age with multiple congenital anomalies (dextrocardia, absent left rib, absent left kidney, undescended left testicle, narrow palpebral fissures, a depressed nasal bridge, and hypoparathyroidism) was admitted because of uncontrolled seizures. He had a prior history of acute otitis media and conjunctivitis. The patient did not have a family history of seizures, birth defects, mental retardation, or learning disabilities. A skin eruption was noted during admission and a dermatology consult was requested. Examination revealed small scattered erythematous papules with a background of mild erythema and superficial scaling on face, trunk, and extremities (Figure 1), but sparing palms and soles. Lymphadenopathy was noted in the axillary and inguinal regions.

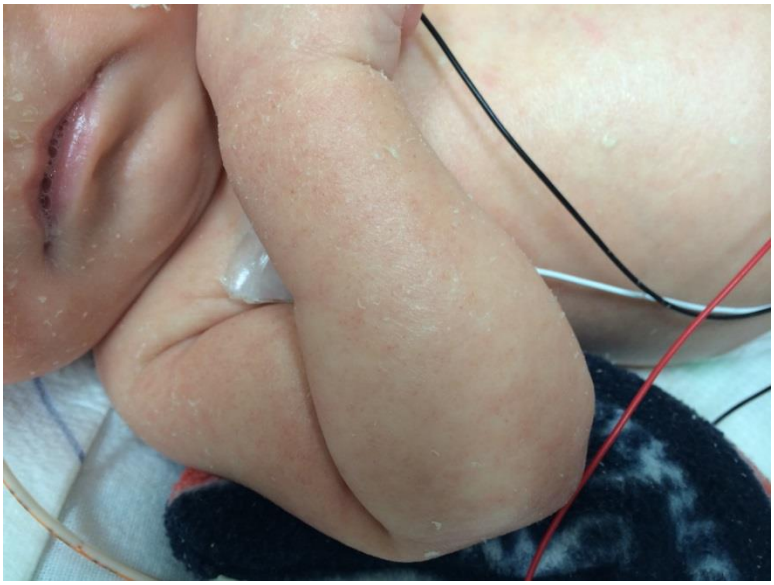

**Figure 1.** Atypical complete DiGeorge syndrome. Dysmorphic facial features include narrow palpebral fissures and a depressed nasal bridge Diffusely scattered erythematous small papules over an erythematous background and fine scale on face, trunk, and extremities.

Laboratory evaluation at admission revealed hypocalcemia with mild increase in serum phosphate levels, as well as eosinophilia (WBC = 5.6 and 13 % eosinophils) and elevated IgE at 329 IU/L (normal < 160 IU/L). Serological screening for human immunodeficiency virus, Epstein-Barr virus, and cytomegalovirus were negative. The patient had a normal 46 XY karyotype, and no deletion in the 22q11.2 region was noted on fluorescence *in situ* hybridization (FISH).

A skin biopsy demonstrated acanthosis and marked spongiosis with exocytosis of lymphocytes. Many of the lymphocytes demonstrated elongated, convoluted nuclei, typical of activation. There was prominent and diffuse parakeratosis with diminished granular cell layer. Scattered intraepidermal neutrophils were seen. A rare dyskeratotic cell was noted at the dermo-epidermal junction. Eosinophils were not striking (Figures 2A and 2B). Within the clinical context, the histopathological findings strongly suggested the diagnosis of atypical complete DiGeorge syndrome (DGS, [1]). Immunophenotype analysis obtained the week of admission showed a normal absolute number of T and B lymphocytes, but absence of naive T-cells, indicating poor thymopoiesis. Oligoclonality of T lymphocytes was demonstrated by an abnormal V-Beta T-cell receptor (TCR) repertoire. To determine whether the oligoclonal T-cells were autologous or of maternal origin, FISH analysis was performed. Probes (Abbott©) for the alpha satellite regions of chromosomes X and Y showed no chimerism. Thus, the diagnosis of atypical complete DGS was confirmed.

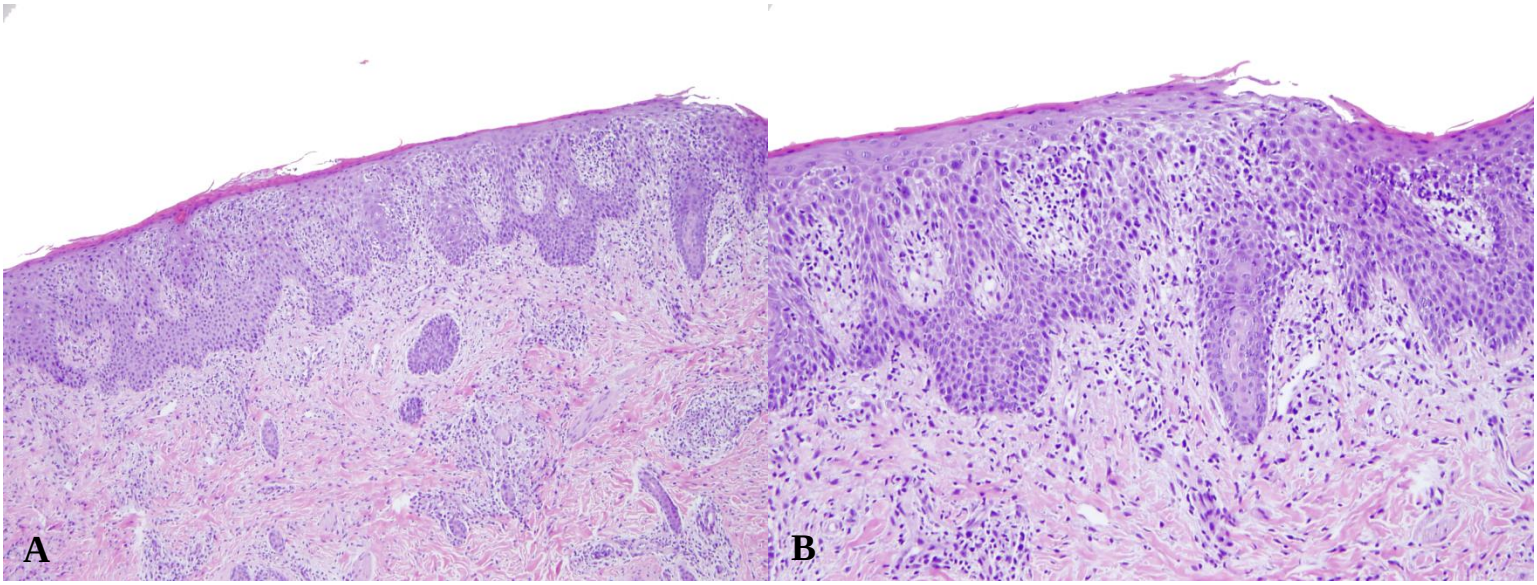


**Figure 2. A.** Histologic sections show diffuse parakeratosis, diminished granular layer, acanthosis, and marked spongiosis (hematoxylin-eosin, original magnification x 40). **B.** Lymphocyte exocytosis. Lymphocytes show elongated, convoluted nuclei, typical of activation. In addition, a rare dyskeratotic cell is observed at the dermo-epidermal junction. (hematoxylin-eosin, original magnification x 400)

Clinically, the seizures were thought to be secondary to hypocalcemia, a common symptom of DGS related to primary hypoparathyroidism. Once the infant received calcium supplementation, the seizures were controlled. The patient was started on cyclosporine and, subsequently, anti-thymocyte globulin was added to control for the aberrant T-cell population affecting different organ systems. Concomitantly, antimicrobial prophylaxis was performed with trimethoprim/sulfamethoxazole, azithromycin, and fluconazole. Within 2 months of this therapy the skin lesions resolved. While awaiting transfer to another institution that performs thymus transplantation, the patient developed tracheitis with *Pseudomonas aeruginosa*, which led to respiratory failure and required subsequent intubation. The antibiotic regimen was modified to intravenous tobramycin, vancomycin, and piperacillin/tazobactam. The anti-thymocyte globulin was discontinued. Despite broad antibiotic coverage he continued with intermittent fevers and worsening respiratory status. He died at 10 months of age from sepsis. At autopsy, both thymus tissue and parathyroid glands were absent.

# Discussion

DGS is a congenital malformation that results from abnormal development of the third and fourth pharyngeal pouches and is commonly associated with a microdeletion at chromosome 22q11.2. However, this deletion is not required to establish a diagnosis. This syndrome is characterized by cardiac anomalies, abnormal facies, thymic hypoplasia, cleft palate, and hypoparathyroidism. Most patients with DGS have minor thymic deficiencies and are classified as having partial DGS. In partial DGS the number of thymic emigrant T-cells increases through time and no intervention is necessary to resolve the initial immunodeficiency. When thymic aplasia is present, the term complete DGS is used. The diagnosis of athymia is demonstrated by showing absence of T-cells (<50/mm3) with a naïve phenotype (CD3+ CD45 RA+ CD62L+) and abnormal T-cell receptor usage either by T-cell receptor spectra typing or FACS analysis of usage of V Beta TCR chains. A small subset of patients with complete DGS may develop an eczematous dermatitis, lymphadenopathy, and an oligoclonal T-cell proliferation. This rare condition is known as atypical complete DGS. Only a few cases have been reported so far [1-7].

Both typical and atypical complete DGS represent third and fourth pharyngeal pouch defects. However, a clinical distinction is that patients with typical complete DGS will not develop the dermatitis with infiltrating T-cells and lymphadenopathy that is characteristic of atypical complete DGS. Furthermore, distinguishing between typical and atypical complete DGS is important with respect to thymus transplantation because T-cells in atypical complete DGS can reject transplants. Indeed, atypical complete DGS requires treatment with immunosuppressive agents to control the oligoclonal T-cell expansion, followed by immune reconstitution via thymic transplantation to correct the severe immunodeficiency [2].

It has been reported that skin lesions and lymphadenopathy develop early and concurrently in patients with atypical complete DGS. These patients also do not show an initial absence of T lymphocytes or systemic manifestations of immunodeficiency [2]. Therefore, the diagnosis of atypical complete DGS is challenging. The clinical presentation may suggest diverse diagnoses, including severe atopic dermatitis, severe combined immunodeficiency, Wiscott-Aldrich syndrome, severe seborrheic dermatitis, erythroderma, maternally-derived graft-vs-host disease (GVHD), and Omenn syndrome [1-7]. Noteworthy, the pathophysiology of Omenn syndrome and atypical complete DGS is similar, i.e., extreme oligoclonality of T-cells. The former produced by a “leaky” severe combined immune deficiency condition often owing to mutations in one of the recombinase genes (RAG1/RAG2), and the latter is owing to near complete aplasia of the thymus, the organ essential for T-cell differentiation [2, 6]. Patients with atypical DGS and Omenn syndrome share oligoclonal expansion of memory T-cells, elevated serum IgE, eosinophilia, diarrhea, and lymphadenopathy. However, these entities can be distinguished by the presence of pharyngeal pouch defects (e.g., hypothyroidism), thymic aplasia, and robust T cell proliferation to phytohaemagglutinin stimulation in DGS [3].

Histological analysis provides helpful clues [1]. Typically, spongiotic dermatitis with satellite cell necrosis, dyskeratosis, and exocytosis of lymphocytes is noted. Parakeratosis, perieccrine and perivascular inflammation, and eosinophils can also be present. The main histopathologic differential diagnoses are spongiotic dermatitis, spongiotic drug reaction, and GVHD. All of these entities may appear strikingly similar, as all may demonstrate the presence of rare eosinophils, necrotic keratinocytes, and varying degrees of spongiosis. The presence of satellite cell necrosis in an immunocompromised population raises the possibility of GVHD. Indeed, cases of maternal engraftment have been seen in patients with DGS [7]. The main histopathologic differences between these two conditions are the prominent epidermal changes (i.e. spongiosis and parakeratosis) in DGS. Spongiotic changes in GVHD, while well-described, are quite rare [8]. As histopathologic features may not unfailingly rule out the above mentioned entities, clinical history is essential for a more definitive diagnosis. In our patient, the lack of administered medications prior to the development of his skin lesions, excluded the possibility of a drug reaction.

In summary, we report the case of an infant with atypical complete DGS, review clinical and histopathologic clues that lead us to diagnostic confirmation of athymia and initiation of therapy. We also highlight the challenges found during his hospitalization before he could be referred to a specialized medical center for transplantation.

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