

Received: 2020.04.09

Accepted: 2020.06.24

Available online: 2020.07.14

Published: 2020.08.26

A Patient with 22q11.2 Deletion Syndrome Presenting with Systemic Skin Rash and Dermatopathic Lymphadenitis of Unusual Histology

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Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, newborn
Final Diagnosis: 22q11.2 deletion syndrome
Symptoms: Congenital heart disease • eczema
Medication: —
Clinical Procedure: —
Specialty: Immunology • Pathology • Pediatrics and Neonatology

Objective: Rare co-existence of disease or pathology
Background: Chromosome 22q11.2 deletion syndrome (22q11.2 DS) currently includes DiGeorge syndrome, conotruncal anomaly face syndrome, and velocardiofacial syndrome. We present the case of a male infant with 22q11.2 DS exhibiting generalized skin rash and dermatopathic lymphadenitis.
Case Report: The patient was born at 40 weeks of gestation with interruption of aortic arch, ventricular septal defect, and thymic defect. Fluorescence *in situ* hybridization method performed on buccal smears detected the deletion of 22q11.2. On day of life 33, diffuse erythema appeared on the entire body. A skin biopsy detected vacuolar interface dermatitis with superficial perivascular infiltration. Laboratory examinations revealed eosinophilia and hypocalcemia. Clinically, cutaneous inflammation was correlated with the abnormal immune response in 22q11.2 DS. On day of life 210, the patient died due to sepsis caused by *Pseudomonas aeruginosa*. An autopsy revealed lymph nodes swellings in the bilateral axillar and subclavicular areas and around the bilateral iliac arteries. Histology of the lymph nodes demonstrated sparse distribution of atrophic germinal centers surrounded by wide zones of proliferating spindle cells, as well as macrophages, Langerhans cells, and interdigitating dendritic cells. Fontana-Masson staining revealed abundant melanin particles in the macrophages. Accordingly, we diagnosed this case as dermatopathic lymphadenitis. Interestingly, CD123 and CD56 double-positive spindle cells also proliferated around the germinal center.
Conclusions: This case had an unusual histological feature of dermatopathic lymphadenitis. Considering the wide variety of unusual immune conditions in 22q11.2 DS, the lymph nodes in the systemic skin inflammation may exhibit an extraordinary histology of spindle cells proliferation.

MeSH Keywords: DiGeorge Syndrome • Lymphadenitis • Skin Diseases, Eczematous

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/924961>



Background

Currently, chromosome 22q11.2 deletion syndrome (22q11.2 DS) includes DiGeorge syndrome (DGS), conotruncal anomaly face syndrome (CTAF), velocardiofacial syndrome, and Opitz G/BBB syndrome and Cayler cardiofacial syndrome when the chromosomal deletion is detected in patients with these syndromes [1]. Most of the patients with the first 2 syndromes and some of the patients with the latter 2 have the chromosomal deletion. The condition 22q11.2 DS is essentially a multi-system syndrome with a remarkable variability in the severity and extent of phenotypic expression in affected patients. We treated a patient who had 22q11.2 DS and manifested generalized skin rash and dermatopathic lymphadenitis (DL) with marked proliferation of spindle-shaped cells. There have been only a few reports on skin rash or erythroderma and lymphadenitis in infants with DGS or 22q11.2 DS [2]. To the best of our knowledge, this is the first report to describe spindle cells proliferation in DL in 22q11.2 DS. We describe the unique microscopic changes and discuss the mechanism of this reaction in the lymph nodes.

Case Report

Clinical summary

A healthy mother gave birth to a male infant with a birth weight 3458 g at 40 weeks of gestation by vaginal delivery. The Apgar scores were 8 and 8 at the 1st and 5th minutes after birth, respectively. A prenatal examination (or ultrasound screening) had indicated that he had interruption of aorta of Celoria Patton classification type B and ventricular septal defect (VSD). Immediately after birth, we found he had no uvula, but he did not have cleft lip or cleft palate. Clinically, no skeletal malformations were detected. On day of life (DOL) 8, bilateral pulmonary artery banding was performed. The thymus was not detected during the surgery or by ultrasonography or chest X-ray. On DOL31, fluorescence *in situ* hybridization method performed on the interphase nuclei of buccal smears detected the deletion of 22q11.2 (data not shown). On DOL33, he developed diffuse eczema throughout the body. Although infantile eczema, contact dermatitis, or viral infection was clinically suspected, laboratory tests could not determine the exact cause. A skin biopsy demonstrated vacuolar interface dermatitis with superficial perivascular infiltration of T-lymphocytes and macrophages (Figure 1A), and laboratory examination revealed eosinophilia (87%) and hypocalcemia (5.7 mg/dL). Finally,

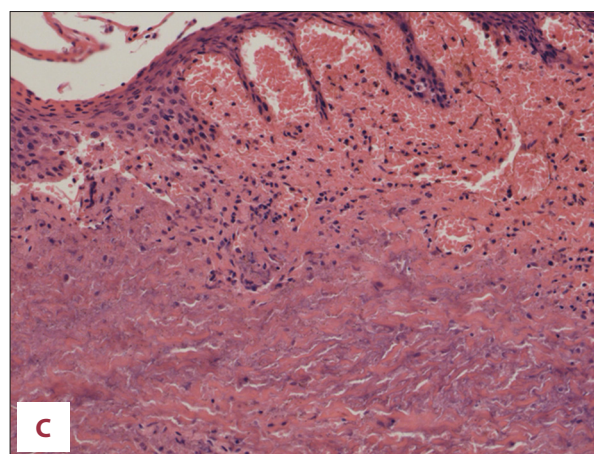
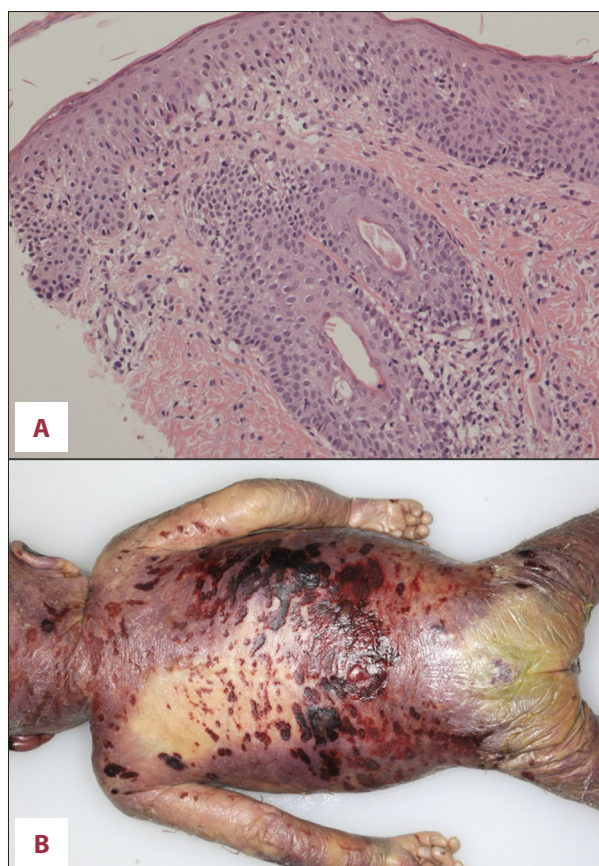


Figure 1. Pathological features of the skin. (A) DOL33, a skin biopsy, demonstrated vacuolar interface dermatitis with superficial perivascular infiltration (hematoxylin and eosin staining (H&E), $\times 75$). (B) Grossly, an autopsy revealed that severe erythroderma with cutaneous erosions and hemorrhages was widely distributed. (C) Microscopically, the epidermis showed an erosive and necrotic change with bacterial infection, and the dermis exhibited severe inflammatory cell infiltration in the autopsy (H&E, $\times 75$).

cutaneous inflammation was considered to have some relationship with the abnormal immune response in 22q11.2 DS. The infant was treated with corticosteroids, but the cutaneous lesions did not ameliorate. On DOL84, lymphocytopenia (lymphocyte count: $0.91 \times 10^9/L$) was observed. Low T cell functions were also confirmed by lymphocyte blast-transformation test induced by phytohemagglutinin and concanavalin A, with 7480 counts per minute (cpm) and 5750 cpm, respectively. Moreover, B cells proportionally decreased, whereas T cells increased, according to flow cytometric analysis. In the T cell population, most were CD8⁺, whereas CD4⁺ T cells were scarce. Most of the T cells were of activated memory type (HLA-DR⁺ and CD45RO⁺). In addition, CD45RA⁺ T cells, which showed recent thymic emigrants, were few. An oligoclonal proliferation of T cells was confirmed by T-lymphocyte receptor repertoire analysis. On DOL74, he suddenly went into shock because of arrhythmia due to hypocalcemia. Laboratory examinations revealed abnormal blood coagulation and elevated liver enzymes, while transthoracic echocardiography detected depressed myocardial contractility. Subsequently, treatment for disseminated intravascular coagulation and heart failure was started. On DOL95, he underwent aortic arch repair and intracardiac repair. Gradually, the cutaneous erosions worsened, and the lymph nodes in the axilla and inguinal regions became swollen. On DOL169, methicillin-resistant *Staphylococcus aureus* was found in the patient's blood culture. On DOL210, the patient died due to sepsis caused by *Pseudomonas aeruginosa* infecting the skin. An autopsy was performed after obtaining informed consent.

Pathological findings

Within 4 hours after death, an autopsy was performed. The systemic skin demonstrated widespread erythroderma with severe cutaneous erosions and hemorrhages (Figure 1B). Microscopically, the epidermis manifested erosive and necrotic change with marked bacterial infection, and the dermis exhibited severe lymphocyte infiltration. Many clefts were formed between the epidermis and the dermis, probably due to severe hemorrhages (Figure 1C).

There were numerous swollen lymph nodes, up to 2.2 cm in size, in the bilateral axillar and subclavicular areas, and around the bilateral iliac arteries (Figure 2). Cut surfaces of the lymph nodes bulged with homogeneously brown discoloration and elastic soft consistency. Histology of the lymph nodes demonstrated a sparse distribution of atrophic germinal centers (Figure 3A). Several centroblasts and centrocytes were observed in the germinal centers, which were not surrounded by mantle zones; instead, they were surrounded by pale zones of proliferating spindle cells (Figure 3B, 3C). The spindle cells consisted of macrophages (positive for CD68 and CD163), Langerhans cells (positive for CD1a, Langerin, and S100p), and



Figure 2. Grossly, several lymph nodes around the bilateral iliac arteries were inflamed, with bulging cut surfaces and homogeneously brown discoloration.

interdigitating dendritic cells (positive for S100p and negative for CD1a and Langerin) (Figure 4A–4I). In addition, some of the spindle cells co-expressed CD123 and CD56 by double immunostaining (Figure 4J–4L). Around the spindle-cell area, there were small lymphocyte aggregates, which were positive for CD3 and CD8 (Figure 4A, 4D); however, neither CD4⁺ lymphocytes (Figure 4C) nor PD1⁺ cells were found. The germinal centers did not contain CD4⁺ and PD1⁺ cells, either. Fontana-Masson staining revealed that the macrophages had numerous melanin particles (Figure 3D). Thus, these lymph nodes were diagnosed as DL.

Macroscopically, the thymic tissue was not detected in the cervix or in the mediastinum. The parathyroid glands were not found macroscopically or microscopically. The lungs (left 49.1 g, right 54.6 g) and liver (282.7 g) demonstrated a systemic inflammatory change. No other anomalies were discovered in the visceral organs.

Discussion

Children with DGS presenting with the clinical triad of immunodeficiency, hyperparathyroidism, and congenital heart disease were originally described in the 1960s [3]. Nowadays, several seemingly unrelated conditions, including DGS, CTAF, and velocardiofacial syndrome, typically result from chromosome 22q11.2 deletion [3]. The main clinical features of 22q11.2 DS include congenital heart defects, palate deformities, facial dysmorphism, developmental delay, and various degrees of immunodeficiency and hypocalcemia. In the present case, aplasia of the thymus and parathyroid glands, anomaly in the heart and major blood vessels, and absence of uvula were manifested; there were no abnormalities other than developmental delay and facial dysmorphisms that we could not completely rule out as the patient was too young.

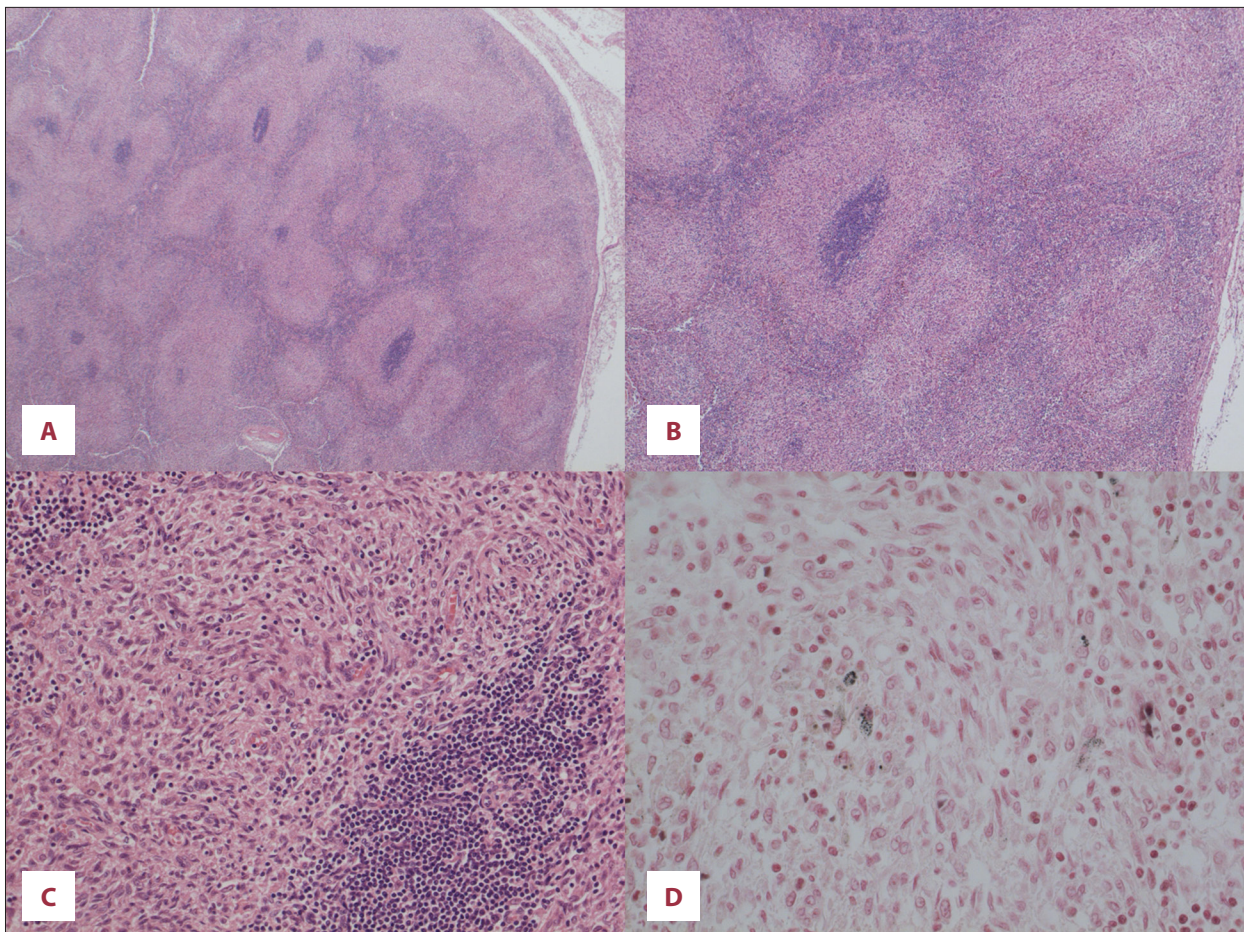


Figure 3. Microscopic features of the lymph node. (A, B) Atrophic germinal centers without mantle zone were sparsely distributed (H&E, $\times 15$, $\times 30$, respectively). (C) The germinal centers were surrounded by many spindle-shaped cells (H&E, $\times 150$). (D) Fontana-Masson staining revealed many melanin particles in the macrophages (Fontana-Masson staining, $\times 300$).

Immunodeficiency affects up to 75% of 22q11.2 DS cases, owing to the hypoplastic thymus or the functional abnormality, which leads to impaired T cell production. 22q11.2 DS has a wide range of T cell deficiency, from normal T cell numbers and function to the absence of T cells [4]. In fact, 1–2% of patients with complete lack of T cells have serious and potentially fatal conditions that are similar to severe combined immunodeficiency [4]. In some 22q11.2 DS cases, an oligoclonal proliferation of T cells has been observed [2]. The present case is consistent with these previous reports, considering that lymphocytopenia, low T cell function, and oligoclonal proliferation of T cells were found.

To date, only a few 22q11.2 DS cases have displayed severe eczema. Minakawa et al. presented a patient with 22q11.2 DS manifesting an itchy eruption, hyper-IgE level, and eosinophilia, mimicking atopic dermatitis [5]. The common association of primary immunodeficiency with allergies and autoimmune diseases raises the question of why immunodeficient patients can develop symptoms suggestive of immune-system

hyperactivation. Recently, regulatory T cells (Tregs), which are a particular subset of T cells, have been implicated in the negative regulation of immune responses and prevention of immunological disorders [6]. Naturally, Tregs develop in the thymus, and FOXP3 genes are considered to play a key role in Treg differentiation. Mutation of the genes results in immune dysregulation-polyendocrinopathy-enteropathy-X-linked syndrome [6], which is characterized by severe eczema, hyper-IgE level, and eosinophilia. Hence, impaired Treg function in primary immunodeficiency can induce immune-system hyperactivation signs, such as severe eczema and eosinophilia, in 22q11.2 DS cases.

Pathological features of the lymph nodes in patients with 22q11.2 DS generally show a depletion of small lymphocytes in the paracortical regions [7], without significant abnormalities in germinal center formation [7]. There have been only a few reports on skin rash or erythroderma and lymphadenitis in infants with DGS or 22q11.2 DS. Markert et al. reported that the lymph nodes of these patients revealed atrophic germinal centers surrounded by CD8⁺ T cells and histiocytes [2];

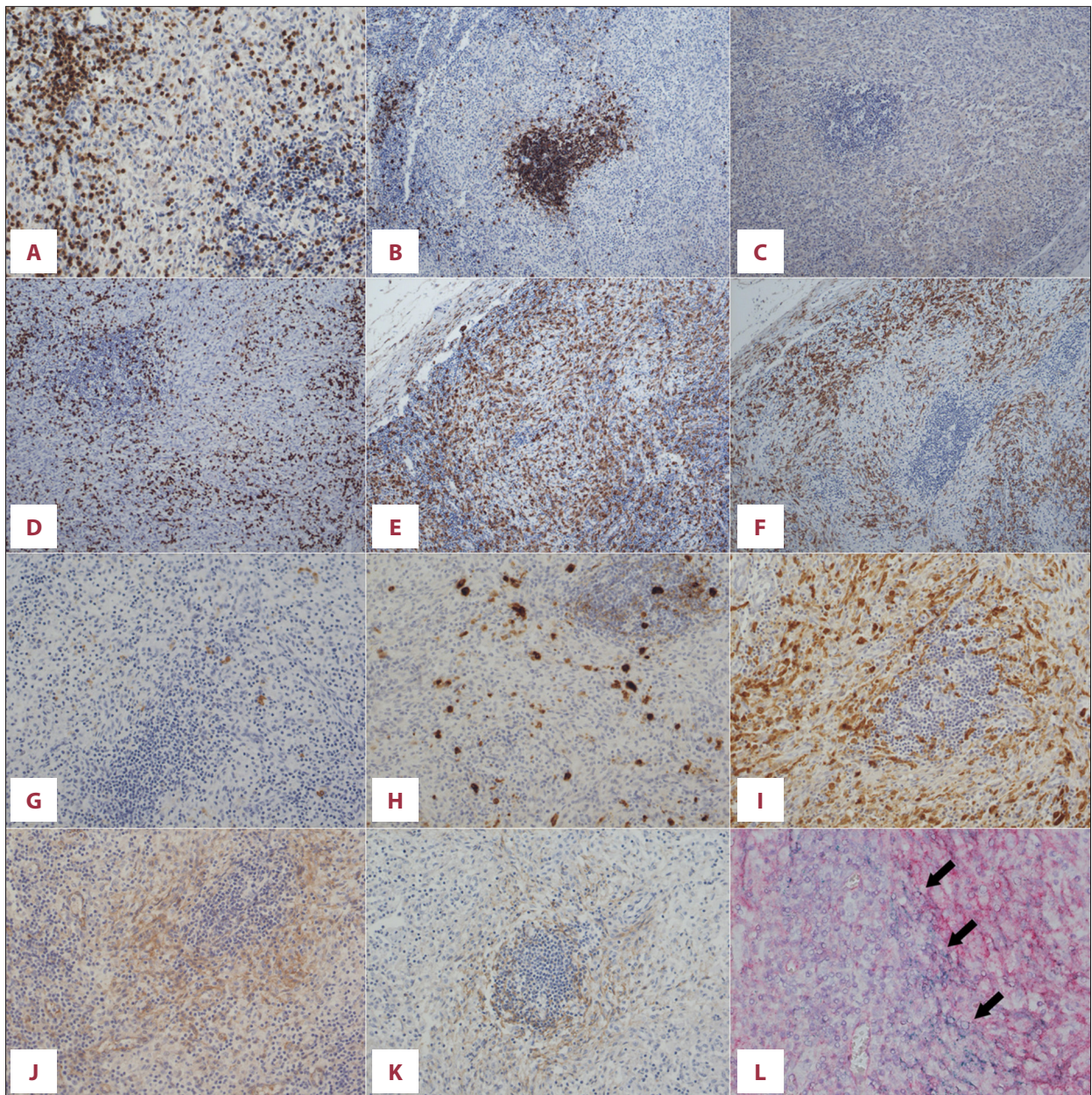


Figure 4. Immunohistochemistry for CD3 (A), CD20 (B), CD4 (C), CD8 (D), CD68 (E), CD163 (F), CD1a (G), Langerin (H), S100p (I), CD123 (J), and CD56 (K) in the lymph nodes. Double immunostaining revealed CD123 (red) and CD56 (blue) co-expression in the PDCs (L, arrows).

they did not describe spindle-cell proliferation in the lymph nodes. To the best of our knowledge, this is the first report concerning spindle cells proliferation in DL in 22q11.2 DS. It is also interesting that DL in most patients (probably without 22q11.2 DS) does not show spindle-cell proliferation, while a nodular expansion of the paracortex by pale-staining macrophages with melanin pigments could be seen [7].

We believed that the marked proliferation of spindle-cell in the lymph nodes in the present patient represented an

extraordinary histology of DL in 22q11.2 DS. The spindle cells mainly consisted of macrophages, Langerhans cells, and interdigitating dendritic cells. Interestingly, some of the spindle cells expressed both CD123 and CD56. Therefore, we supposed some of them had the immunohistochemical phenotype of plasmacytoid dendritic cells (PDCs). However, we could not determine the cell lineage of the CD123 and CD56 double-positive cells, because in addition to PDCs, CD123 is expressed on other several cells such as myeloid lineage cells and activated T cells, among others. Further experiments are needed

to confirm the cell lineage. In the present case, thymic agenesis and T cell immunodeficiency led to an abnormal immune status. Given this unusual immune condition in 22q11.2 DS, lymph nodes in the systemic skin inflammation may show an extraordinary histology of increased proliferation of spindle cells around the atrophic germinal center.

Conclusions

DL in the present 22q11.2 DS patient demonstrated unusual histological features. The marked proliferation of spindle-shaped cells is a unique finding that has not been reported before in the English literature. Hence, accumulation of cases and further investigations are necessary to confirm the precise pathogenesis of these characteristic changes.

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Acknowledgments

We express our sincere thanks to Dr. Masaru Kojima, professor, Dokkyo Medical University School of Medicine, and Dr. Makoto Naito, professor emeritus, Niigata University Graduate School of Medical and Dental Sciences, for collaboration on this work. We are grateful to all the staff of the Department of Clinical Laboratory, Seirei Hamamatsu General Hospital for technical assistance.

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