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Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a drug-induced severe adverse reaction that most often involves the skin. Drug-induced hypersensitivity syndrome/DRESS (subsequently referred to as DRESS) can be life-threatening, with cutaneous and internal organ involvement and a mortality rate of about 10%. Because cases may be underrecognized because of the variable clinical and laboratory features, the incidence of DRESS remains unclear, with an estimated overall population risk of at least 10 cases per million per year. Historically, DRESS was observed initially in patients receiving anticonvulsants in the 1930s. Subsequently, a case of fever, exfoliative dermatitis, and hepatitis after taking phenytoin was reported in 1950 and was referred to as Dilantin hypersensitivity. In 1996, Bocquet et al proposed the term DRESS, along with a concise description of the syndrome. Reactivation of human herpesvirus (HHV)-6 was identified in patients with DRESS syndrome in 1997. The reported incidence of lymphadenopathy in patients with DRESS syndrome ranges from 31% to 88%. However, papers describing the pathologic findings of lymph nodes in patients with DRESS are limited in the literature. Importantly, the morphologic findings in DRESS syndrome can be florid and resemble, in part, lymphomas.
Here, we describe a case series of 5 patients diagnosed with DRESS-related lymphadenopathy and present a literature review. We provide detailed clinicopathologic features of these patients and describe 3 patients who had morphologic features reminiscent of angioimmunoblastic T-cell lymphoma (AITL), which we refer to as AITL-like pattern. We also discuss the differential diagnosis between AITL-like DRESS lymphadenopathy and genuine AITL.

**MATERIALS AND METHODS**

**Study Cohort**

We enrolled 5 cases of DRESS syndrome from the archives of National Cheng Kung University Hospital, Tainan, Taiwan (cases 1, 2, and 4) and consultation files of 1 author (cases 3 and 5). The diagnosis of DRESS was based on the diagnostic criteria for DRESS developed by the Registry of Severe Cutaneous Adverse Reaction group or diagnostic criteria for DIHS/DRESS established by a Japanese consensus group.2 This study was approved by the institutional review board (A-ER-110-037 and CE21178B) and was in accord with the Helsinki Declaration of 1975, as revised in 2013.

**Histologic and Immunohistochemical Stains**

Hematoxylin–eosin–stained tissue sections were cut and prepared from formalin-fixed, paraffin-embedded tissue blocks. Immunohistochemical analysis was performed using 4-μm-thick tissue sections deparaffinized with xylene. The procedures were performed using an automated immunohistochemistry stainer (BenchMark XT, Ventana Medical Systems, Inc, Tucson, Arizona). The primary antibodies and working dilutions are listed in the Supplemental Table (see supplemental digital content). Appropriate positive and negative controls were used.

**In Situ Hybridization for Epstein-Barr Virus–Encoded RNA**

In situ hybridization was performed to detect Epstein-Barr virus–encoded small RNA (EBER) using a polymerase chain reaction (PCR)–derived digoxigenin-labeled DNA probe.25 The test for nucleotide integrity was performed by using an RNA positive control probe (Ventana Medical Systems, Inc). The intended target is the polyA tail in messenger RNA found in nuclei. The EBER in situ hybridization was deemed positive when there were more than 10 EBER nuclei per 0.5 cm² (≥0.2/mm²).26-28

**Sample Preparation and DNA Extraction**

Genomic DNA was extracted from 10-μm-thick sections prepared from formalin-fixed, paraffin-embedded tissue blocks and was purified using a kit (DNeasy Blood & Tissue Kit, Qiagen Inc, Valencia, California). The tissue sections were washed first with phosphate-buffered saline (pH 7.2) to remove fixative and then deparaffinized with xylene and washed twice with ethanol. After extraction, DNA was stored at −20°C until analysis.

**T-Cell Clonality Analysis by PCR**

Multiplex PCR protocols and primers were used for analysis of TRB and TRG following standardized BIOMED-2 protocols, as described previously.29 DNA quality of the specimens was assessed using the multiplex PCR reaction for internal control DNAs. A T-cell lymphoma was used as positive control and water was used as a negative control.

**Detection of HHV-6 by PCR**

We assessed for HHV-6 viral DNA in lymph node tissues using a PCR-based method with a commercial kit for HHV-6 detection (TIB Molbiol, Berlin, Germany) following the manufacturer’s instructions. A 272-bp fragment of the antigenic virion protein 101K (UL11) gene of the HHV-6 genome was amplified with specific primers. The resulting PCR fragment was analyzed with hybridization probes and detected in channel 640.

| Age, y/sex (mean age, 40.8 y) | 29/M | 55/M | 59/F | 23/M | 38/M |
|-----------------------------|------|------|------|------|------|
| Fever >38.5°C                | +    | +    | +    | +    | +    |
| Enlarged lymph nodes         | +    | +    | +    | +    | +    |
| Eosinophilia (>0.7 × 10³/mm³)| 1.59 | 23.5 | 2.61 | 0.77 | 0.85 |
| Leukocytosis (>9.5 × 10³/mm³)| +    | +    | +    | +    | +    |
| Atypical lymphocytosis       | +    | +    | +    | +    | +    |
| Abnormal liver function      | +    | +    | +    | +    | +    |
| LDH elevation (>225 U/L)     | +    | +    | +    | +    | +    |
| Organ involvement            | +    | +    | +    | +    | +    |
| Skin rashes                  | +    | +    | +    | +    | +    |
| Rash resolution >15 d        | +    | +    | +    | +    | NA   |
| ANA                          | ND   | ND   | ND   | ND   | –    |
| ANCA                         | ND   | ND   | ND   | ND   | –    |
| Skin biopsy suggesting DRESS | +    | +    | ND   | ND   | NA   |
| Duration of illness, wk      | 4    | 14   | 16   | 3    | 5    |

Table 1. Summary of Clinicopathologic Features in 5 Cases With Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)

**RESULTS**

**Clinical Features**

The study group was composed of 5 patients, 4 men and 1 woman, with ages ranging from 23 to 59 years (mean, 41 years). All patients were hospitalized and had fever, enlarged lymph nodes, eosinophilia, and organ involvement mainly with liver function abnormalities. Four of the 5 patients (80%) had a skin rash and elevated serum levels of lactate dehydrogenase. Patient 5, although he did not have a skin rash, still fulfilled the criteria of atypical DIHS/DRESS established by a Japanese consensus group.13 Three patients (60%) had leukocytosis and atypical lymphocytosis in the peripheral blood. Serology tests for anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were carried out in 4 and 2 cases, respectively, and all were negative. Patients 1 and 2 underwent skin biopsy, which showed pathologic features suggestive of DRESS: one was purpuric superficial perivascular dermatitis with scattered eosinophils, and the other was purpuric interface dermatitis, compatible with drug eruption.14 The clinical features, including duration of illness, are summarized in Table 1. One patient (case 2) died of septic shock. Blood cultures prior to death yielded *Klebsiella pneumoniae* and *Elizabethkingia meningoseptica*.

**Histopathologic Features**

Three lymph node biopsy specimens (cases 1–3) showed a pattern reminiscent of AITL (AITL-like pattern) and 2 cases showed necrotizing lymphadenitis (Kikuchi-like pattern), associated with vasculitis in 1 case (case 5). The morphologic features, including results of special studies, are summarized in Table 2.

The AITL-like pattern (n = 3) revealed nearly total effacement of nodal architecture by a dense polymorphic infiltrate with pale appearance (Figure 1, A, case 1; B, case 2; and C, case 3). The infiltrate was composed of small and
medium-sized lymphoid cells and eosinophils admixed with some immunoblasts in a background rich in high-endothelial venules, which showed an arborizing pattern (Figure 1, D). Some clear cells infiltrating around blood vessels were noted in 2 cases. The infiltrating lymphocytes including clear cells showed mild nuclear atypia (Figure 1, E). Immunohistochemical analysis showed increased T cells in interfollicular areas (Figure 2, A) with minimal CD20-positive B cells (Figure 2, B). There was T-zone expansion but no T-cell nodules. The atypical lymphocytes were positive for CD2, CD3, CD4, CD7, βF1, and CD30 (some) and negative for CD8, CD10, CD20, BCL6, and PD-1. The CD4:CD8 ratio was 5:1 to 6:1 in the T-cell infiltrates (Figure 2, C and D). Expansion of follicular dendritic cell meshwork as demonstrated by CD21 or CD23 immunostaining was absent in all 3 cases (Figure 2, A). The CD30 antibody highlighted some immunoblasts in B-cell areas in 2 cases (Figure 2, C and D). Expansion of follicular dendritic cell meshwork was noted by CD21 or CD23 immunostaining. The Kikuchi-like pattern (n = 2) showed interfollicular expansion by several foci of necrosis composed of karyorhectic debris and fibrin deposits surrounded by histiocytes (case 4; Figure 3, A). There was also infiltration of small and large lymphocytes, histiocytes, and some apoptotic cells indicative of plasmacytoid dendritic cells (case 4; Figure 3, B). Plasma cells and eosinophils were inconspicuous. Residual lymphoid follicles were also present. Immunohistochemical analysis showed that the interfollicular infiltrate was expanded by CD3-positive T cells, and aggregates of plasmacytoid dendritic cells were highlighted by the antibody specific for CD123 (Figure 3, C). In case 5, vascular hyperplasia was additionally noted in the interfollicular region (Figure 3, D). These blood vessels around the necrotic patches showed fibrinoid material and nuclear dust suggestive of vasculitis (Figure 3, E). In addition, hemophagocytosis in sinusoids was discerned. By immunohistochemistry, the infiltrating cells were composed predominantly of CD3-positive cells and a small subset of CD20-positive cells. Among the T cells, CD4-positive cells outnumbered CD8-positive cells. Around 10% to 20% of CD4-positive T cells expressed CD25 (Figure 3, F). Interspersed histiocytes and activated larger cells were highlighted by CD68 and CD30 stains, respectively. Immunostaining for herpes simplex virus–1/2 and HHV-8 was negative.

Table 2. Summary of Pathologic Features of Lymph Node Biopsy

| Morphology of lymph node | Patient No. | 1 | 2 | 3 | 4 | 5 |
|--------------------------|------------|---|---|---|---|---|
| Lymph node effacement    | AITL-like  | AITL-like | AITL-like | Kikuchi-like | Kikuchi-like |
| Polymorphic infiltrate   | +          | +          | +          | –          | –          |
| Clear cells              | +          | +          | +          | –          | –          |
| Nuclear atypia           | +          | +          | +          | –          | –          |
| Eosinophilic infiltration| +          | +          | +          | –          | +          |
| High-endothelial venules | +          | +          | +          | –          | +          |
| Necrotic foci            | –          | –          | –          | +          | +          |
| Vasculitis               | –          | –          | –          | –          | +          |
| Hemophagocytosis         | +          | –          | –          | –          | +          |

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; BM, bone marrow; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; NA, not available; ND, not done; pDCs, plasmacytoid dendritic cells; TCR, T-cell receptor; +, present; –, absent.
Figure 1. Drug reaction with eosinophilia and systemic symptoms lymphadenopathy with features reminiscent of angioimmunoblastic T-cell lymphoma (cases 1–3). A, Case 1 shows nearly total effacement of nodal architecture by a dense polymorphic infiltrate with pale patchy appearance. B, Case 2 also shows nodal effacement by a polymorphic infiltrate with evident clear cells and proliferations of high endothelial venules. C, Case 3 shows a similar picture with partial effacement of nodal architecture by a polymorphic infiltrate containing a higher number of histiocytes. D, There are increased numbers of arborizing high-endothelial venules. E, The infiltrate is composed of lymphocytes, histiocytes, immunoblasts, and eosinophils; some lymphocytes with clear cytoplasm show nuclear atypia (arrows) (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B and C], ×400 [D], and ×1000 [E]).
Figure 2. Immunohistochemical findings of angioimmunoblastic T-cell lymphoma–like drug reaction with eosinophilia and systemic symptoms lymphadenopathy. A and B, CD3 staining shows increased T cells in interfollicular areas with minimal CD20-positive B cells in between. There is T-zone expansion but no T-cell nodules. C and D, The infiltrating T cells are composed predominantly of CD4-positive cells, with a CD4:CD8 ratio of 5:1 to 6:1 (C, CD4; D, CD8). E, CD21 staining shows no expansion of follicular dendritic cell meshwork in the T-cell infiltrate. F, CD30 antibody highlights some large transformed cells in B-cell area (original magnifications ×100 [A through E] and ×1000 [F]).
Figure 3. Drug reaction with eosinophilia and systemic symptoms lymphadenopathy with features reminiscent of Kikuchi disease (cases 4 and 5). A, In case 4, the lymph node shows interfollicular expansion with several residual lymphoid follicles. B, The interfollicular expansion reveals a polymorphic infiltrate, which is characterized by small and large lymphocytes, histiocytes, and some apoptotic cells. C, There are aggregates of plasmacytoid dendritic cells demonstrated by CD123 staining. D, Case 5 shows similar interfollicular expansion characterized by pale pink appearance with vascular proliferation. E, At higher magnification, there is prominent vasculitis featuring fibrinoid necrosis and karyorrhexis in the vascular lumens. F, CD25 staining highlights 10% to 20% of positive cells in a background composed mainly of CD4-positive T cells (hematoxylin-eosin, original magnifications ×40 [A], ×200 [D], ×400 [C and E], and ×1000 [B]; original magnification ×400 [F]).
Molecular Analysis

In all 5 cases, in situ hybridization for EBER was performed. In 1 patient specimen (case 3), scattered EBER-positive cells were identified. Molecular studies to assess the T-cell receptor genes were negative in all 4 cases assessed (cases 1–3 and 5). All 5 cases were negative for HHV-6 DNA by PCR on lymph node specimens.

Literature Review

In summary, all 5 cases we report fulfilled the Registry of Severe Cutaneous Adverse Reaction/Japanese DIHS criteria for DRESS/DIHS. In the literature, 10 cases of DRESS-related lymphadenopathy with mention of lymph node morphology have been described (Table 3). Patient age ranged from 16 to 58 years (mean, 34 years) and the male to female ratio was 3:7. The culprit drugs and clinical data including leukocyte counts, serum liver function enzymes, and lactate dehydrogenase levels are listed (Table 3). Polymerase chain reaction analysis to detect HHV-6 in lymph node tissues was performed in 4 cases, and 3 were positive. The patient with negative PCR results had an elevated serum titer for HHV-6 immunoglobulin G antibody. Morphologic evaluation of these cases showed 6 with features reminiscent of T-cell lymphoma (n = 5) or atypical T-cell proliferation (n = 1). Other lymph node specimens showed Hodgkin lymphoma–like features (n = 2), necrotizing lymphadenitis (n = 1), reactive lymphoid hyperplasia (n = 1) and dermatopathic lymphadenopathy (n = 1). Clinical follow-up of these patients showed that 1 patient died and the overall mortality rate was 10%.

DISCUSSION

Although the incidence of DRESS syndrome is not uncommon, the pathologic features of DRESS-associated lymphadenopathy have been mentioned rarely in the literature. Table 3, we summarize the morphologic patterns described in previous cases and the 5 cases reported here. Over half of all cases reported previously had T-cell lymphoma–like morphologic features, perhaps because of the selection bias of accepted reports. The most frequent morphologic features of DRESS-associated lymphadenopathy, mimicking T-cell lymphoma, include marked expansion of the paracortex with distortion of lymph node architecture and the presence of a mixed inflammatory background with eosinophils. Atypical immunoblasts with Reed-Sternberg–like cells were present in 2 cases. Decreased expression of pan–T-cell antigens, including CD3 and CD7, has been reported in some cases. These features may raise concerns or further suggest a diagnosis of lymphoma, especially AITL.

Two of the 5 cases we report showed morphologic features similar to necrotizing lymphadenitis (Kikuchi disease–like); 1 of these biopsy specimens also showed vasculitis. The lymph node architecture was relatively preserved with patches of necrosis and nuclear dust. Sinusoidal areas were dilated by histiocytes showing hemophagocytosis. No evidence of infection or granuloma formation was present. Although drug-induced or drug-associated vasculitis usually attacks the skin and sometimes lungs and kidneys, some T-cell proliferations with effacement of the nodal architecture. There were dense and massive infiltrates of polymorphic and atypical lymphocytes around hyperplastic high-endothelial venules. Some atypical cells with clear cytoplasm were evident.

The 3 cases with AITL-like features we report highlight that the differential diagnosis of true AITL versus DRESS lymphadenopathy can be highly challenging. The neoplastic cells of AITL typically express markers of follicular helper T cells such as CD10, BCL6, PD-1, ICOS, CXCL13, and CXCR5. In situ hybridization for EBER commonly shows many Epstein-Barr virus–positive immunoblasts of B-cell lineage, and usually clonal T-cell receptor gene rearrangements and RHAO mutations are present. In contrast, DRESS-related lymphadenopathy is mediated by expansion of regulatory T cells. Regulatory T cells are a subpopulation of CD4-positive T cells characterized by overexpression of FOXP3 and CD25. Lymphadenopathy related to DRESS is frequently negative for Epstein-Barr virus–positive cells by in situ hybridization and there is no evidence of clonal rearrangement of the T-cell receptor genes. Clinical information is also important for this differential diagnosis, including history of drug exposure (Naranjo score), age, and the absence of other AITL-associated symptoms such as hemolytic anemia and hypergammaglobulinemia. Finally, molecular analysis of the T-cell receptor genes rearrangement will reveal a polyclonal pattern in DRESS-related lymphadenopathy.

The diagnostic criteria of DRESS syndrome are skin rash, eosinophilia, atypical lymphocytes, liver abnormalities, and lymphadenopathy. Hence, the clinical differential diagnosis may include connective tissue disorders, idiopathic hypereosinophilia, viral hepatitis, Churg-Strauss syndrome, and Kimura disease. A detailed clinical history, including anti-nuclear antibody and anti-neutrophil cytoplasmic antibody serology tests, would be very helpful to reach a correct diagnosis of DRESS syndrome and exclude other entities such as idiopathic hypereosinophilia, viral hepatitis, and Kimura disease. In addition, the pathologic features of lymph node biopsy in Churg-Strauss syndrome and Kimura disease are also characteristic. The reported pathologic features of nodal Churg-Strauss syndrome are broad, including lymphoid and plasmacytic hyperplasia, hyperplasia with eosinophilia, and hyperplasia with allergic granulomas. Although the latter is the pathognomonic feature of Churg-Strauss syndrome, lymphoid hyperplasia with eosinophilia may be found in drug-induced lymphadenopathy. In these cases, clinical history is of paramount importance for differentiation. Kimura disease typically presents with eosinophilia and multiple lymphadenopathies predominantly in the head and neck region, which may be one of the differential diagnoses of DRESS syndrome clinically. However, pathologically, Kimura disease is characterized by follicular and interfollicular hyperplasia accompanied with eosinophils and eosinophilic microab-scesses within the germinal centers. These findings are distinct from those found in DRESS lymphadenopathy. On the other hand, the Kikuchi-like morphology in our 2 cases may raise the possibility of lupus lymphadenopathy. In addition to a negative anti-nuclear antibody test and other clinical manifestations, it has been recently found that lupus lymphadenopathy shows a higher frequency of plasma cell infiltration and positive C4d endothelial staining in the
| Age, y/SEX | MEDICATION/DURATION | LABORATORY DATA | VENOUS MORPHOLOGY | CLINICAL MORPHOLOGY | FOLLOW-UP | SOURCE |
|-----------|---------------------|-----------------|-------------------|---------------------|----------|--------|
| 33/F      | Sulfasalazine/2 wk  | AST/ALT: 52/121 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | Johnson et al, 2013 |
| 57/F      | Carbamazepine/1 mo | AST/ALT: 81/144 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | Saraya et al, 2013 |
| 3/8/F     | Phenobarbital/14 d  | AST/ALT: 8/14 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | Cohen et al, 2003 |
| 48/M      | Allopurinol/2 wk    | AST/ALT: 413/784 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | This study |
| 27/F      | Carbamazepine/1 mo | AST/ALT: 50/121 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | This study |
| 31/M      | Vancomycin/3 wk     | AST/ALT: 1305/672 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | This study |
| 59/F      | Temozolomide/20 d   | AST/ALT: 406/406 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | This study |
| 38/M      | Antibiotics/3 wk    | AST/ALT: 50/100 U/L | Atypical lymphocytes | T-cell lymphoma-like | Recovery | This study |

**Abbreviations:** AITL, angioimmunoblastic T-cell lymphoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBV, Epstein-Barr virus; eos, eosinophils; HHV, human herpesvirus; IgG, immunoglobulin G; ISH, in situ hybridization; LDH, lactate dehydrogenase; NA, not available; PCR, polymerase chain reaction; WBC, white blood cells.
necrotic area.37 Accordingly, the lymph nodes in cases 4 and 5 showed inconspicuous plasmacytic infiltration and were negative for Cd4 endothelial staining.

In this study, all 5 patients presented initially with fever, lymphadenopathy, and laboratory abnormalities, fulfilling the diagnostic criteria of DRESS.25-27 However, HHV-6 was not detected in any of the 5 lymph nodes in this study, in contrast to 3 of 5 cases positive in previous reports (Table 3). The cause for this discrepancy is unclear. So far, there is no other report from Taiwan regarding the prevalence of HHV-6 in DRESS lymph nodes, but one Taiwan study showed HHV-6 DNA can be detected in 1 of 19 serum samples (5.3%) from DRESS patients.38 A similar low HHV-6 detection rate (1 of 24; 4.2%) has been reported from the serum of patients with DRESS in the United States.39 Interestingly, a higher positive rate of HHV-6 reactivation (30%–50%) can be observed in whole blood by PCR methods or by assessment of serologic antibody titers, that is, at least 4-fold elevations of anti-HHV-6 antibodies.40 It appears that the discrepancy of HHV-6 detection rates among different reports may be attributable to differences in patient populations, timing for detecting viral reactivation (within versus beyond 4 weeks after the initial diagnosis), and, most importantly, detection methods with samples used (serology versus PCR and serum versus whole blood).39,40 On the contrary, given that expansion of herpesviruses,13 other viruses than HHV-6 may alternatively play a role. Accordingly, we have detected Epstein-Barr virus genome in 1 case of nodal tissue by situ hybridization.

Although DRESS syndrome is uncommon in its incidence, this syndrome is associated with significant morbidity and mortality. The most important management is immediate discontinuation of the culprit medication.41 A timely diagnosis and prompt treatment significantly affects the prognosis of patients with DRESS syndrome. Further treatment with systemic corticosteroids or other immunosuppressants may be required at the acute phase.2 At the later phase, preventing the subsequent development of infection such as sepsis, cytomegalovirus, and autoimmune diseases is mandatory.2 Although the prognosis of patients with DRESS syndrome is variable and unpredictable, most patients recover completely after drug withdrawal and appropriate therapy. The overall mortality rate of patients with DRESS syndrome is approximately 10%, primarily from visceral organ complications.41

In conclusion, DRESS-associated lymphadenopathy is an uncommon biopsy specimen encountered by pathologists that can be diagnostically challenging, as these lymph nodes can frequently show morphologic features closely resemblingAITL. A high index of suspicion and knowledge of the clinical history are essential for diagnosis. Ancillary studies are also very helpful in this differential diagnosis. Unlike trueAITL, lymph nodes involved by DRESS syndrome usually have expanded regulatory T cells and lack EBER-positive B cells or clonal T-cell receptor gene rearrangements.

References
1. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010;146(12):1373–1379.
2. Shioura T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DisHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. Allergol Int. 2019;68(3):301–308.
3. Merritt HH, Putnam TJ. Sodium diphenyl hydantoinate in the treatment of convulsive disorders. JAMA. 1938;111(12):1068–1073.
4. Chaiken BH, Goldberg BI, Selag JP. Dilantin sensitivity—report of a case with jaundice, pyrexia and exfoliative dermatitis. N Engl J Med. 1950;242(23):897–898.
5. Magneau H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250–257.
6. Descamps V, Bouscarat F, Lagレンene S, et al. Human herpes virus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemopagocytic syndrome. Br J Dermatol. 1997;137(4):605–608.
7. Walsh S, Diaz-Cano S, Higgins E, et al. Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome?: a review of clinicopathological features of 27 cases. Br J Dermatol. 2013;168(2):391–400.
8. Chang KC, Khen NT, Jones D, et al. Epstein-Barr virus is associated with all histotogical subtype of Hodgkin lymphoma in Vietnamese children with special emphasis on the entity of lymphocyte predominance subtype. Hum Pathol. 2005;36:753–755.
9. Chen YP, Jones D, Chen YT, et al. Epstein-Barr virus present in T cells or B cells shows differential effects on hemophagocytic symptoms associated with outcome in T-cell lymphomas. Leuk Lymphoma. 2014;55(9):2038–2047.
10. Chen YK, Yen YJ, Wang MC, et al. A newly recognized histologic pattern of IgG-related lymphoproliferative disease, expanding the morphologic spectrum. Am J Surg Pathol. 2018;42(7):977–982.
11. Dojcinov SD, Venkatakrishnan G, PillaiG S, et al. Age-related EBV-associated lymphoproliferative disorders in the Western population: a spectrum of reactive lymphoid hyperplasia and lymphoma. Blood. 2011;117(18):4726–4735.
12. Chen YL, Su IJ, Cheng HY, et al. BIOMED-2 protocols to detect clonal immunoglobulin and T-cell receptor gene rearrangements in B- and T-cell lymphomas in southern Taiwan. Leukemia. 2001;15(1):650–655.
13. Shioura T, Kano Y. Drug reaction with eosinophilia and systemic symptoms (DRESS): incidence, pathogenesis and management. Expert Opin Drug Saf. 2017;16(2):139–147.
14. Cho YT, Liu YJ, Chang CY, et al. Co-existence of histopathological features is characteristic in drug reaction with eosinophilia and systemic symptoms and correlates with high grades of cutaneous abnormalities. J Eur Acad Dermatol Venereol. 2016;30(12):2077–2084.
15. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. Int J Mol Sci. 2017;18(6):1243.
16. Cohen Y, Rund D, Moualem E, et al. Carbamazepine-induced generalized “pseudoalleskemia lymphoma”–like disease. Isr Med Assoc J. 2003;5(6):457.
17. Subhanman K, Gajpal J. Necrotizing lymphadenitis associated with the phenytoin-induced hypersensitivity syndrome. South Med J. 2003;96(9):937–939.
18. Nawaz F, Wall BM. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome: suspected association with titanium bioapatosis. Am J Med Sci. 2004;327(4):215–218.
19. Saraya T, Mikoshiha M, Kamiyama H, et al. Evidence for reactivation of human herpes virus 6 in generalized lymphadenopathy in a patient with drug-induced hypersensitivity syndrome. J Clin Microbiol. 2013;51(6):1979–1982.
20. Gowani F, Gehrs B, Scordino T. Drug-induced hypersensitivity syndrome: a clinical, pathologic, and histologic mimic of lymphoma. Case Rep Hematol. 2018;2018:7037352.
21. Schnetzke U, Bossert T, Scholl S, et al. Drug-induced lymphadenopathy with eosinophilia and renal failure mimicking lymphoma disease: dramatic onset of DRESS syndrome associated with antibiotic treatment. Ann Hematol. 2011;90(11):1353–1355.
22. Mine S, Suzuki K, Sato Y, et al. Evidence for human herpesvirus-6B infection of regulatory T cells in acute systemic lymphomas in an immunocompetent adult with the drug reaction with eosinophilia and systemic symptoms syndrome: a case report. J Clin Viral. 2014;61(3):448–452.
23. Sato R, Itoh M, Suzuki H, et al. Pathological findings of lymphadenopathy in drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic syndrome (DRESS): similarities with angioimmunoblastic T-cell lymphoma. Eur J Dermatol. 2017;27(2):201–202.
24. Rim MV, Hong J, Yo I, et al. Cervical lymphadenopathy mimicking angioimmunoblastic T-cell lymphoma after daspamon-induced hypersensitivity syndrome. Korean J Pathol. 2012;46(6):606–610.
25. Johnson S, Mathews S, Hudnall MD. Human herpesvirus 6 lymphadititis in Drug rash with eosinophilia and systemic symptoms syndrome: a lymphoma mimic. Histopathology. 2017;70(7):1166–1170.
26. Pinto B, Dhir V, Krishnan S, et al. Leflunomide-induced DRESS syndrome with renal involvement and vasculitis. Clin Rheumatol. 2013;32(5):689–693.
27. Radic M, Martinovic Kaliterna D, Radic I. Drug-induced vasculitis: a clinical and pathological review. Neth J Med. 2012;70(1):12–17.
28. Weiss LM, Jaffe ES, Liu XF, et al. Detection and localization of Epstein-Barr virus in T lymphomas in southern Taiwan. Leuk Lymphoma. 2003;47(1):179–179.
29. Hu YS, Wang YC, Chen CY, et al. Angioimmunoblastic T-cell lymphoma in Taiwan reveals worse progression-free survival for RHOA G17V mutated subtype. Leuk Lymphoma. 2010;60(5):1108–1118.
30. Sakaguchi S, Wing K, Onishi Y, et al. Regulatory T cells: how do they suppress immune responses? *Int Immunol*. 2009;21(10):1105–1111.
31. Shevach EM. Mechanisms of Foxp3+ T regulatory cell-mediated suppression. *Immunity*. 2009;30(5):636–645.
32. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. *Nat Rev Immunol*. 2008;8(7):523–532.
33. Jeong J, Sim DW, Yu JE, et al. Differentiation of angioimmunoblastic T-cell lymphoma from DRESS syndrome. *J Allergy Clin Immunol Pract*. 2019;7(5):1684–1686.e1.
34. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Rev 4th ed. Lyon, France: IARC; 2017.
35. Garcia Carretero R, Romero Brugera M, Rebollo-Aparicio N, et al. Eosinophilia and multiple lymphadenopathy: Kimura disease, a rare, but benign condition. *BMJ Case Rep*. 2016.
36. Swanson EJ, Manivel JC, Valen PA, et al. Necrotizing eosinophilic granulomatous lymphadenitis with ring- and C-shaped granulomas—an under-recognized specific manifestation of nodal Chung-Strauss syndrome. *J Hematopathol*. 2017;10(1):39–45.
37. Yu SC, Chang KC, Wang H, et al. Distinguishing lupus lymphadenitis from Kikuchi disease based on clinicopathological features and C4d immunohistochemistry. *Rheumatology (Oxford)*. 2021;60(3):1543–1552.
38. Chen YC, Chuang HH, Cho YT, et al. Human herpes virus reactivations and dynamic cytokine profiles in patients with cutaneous adverse drug reactions—a prospective comparative study. *Allergy*. 2015;70(5):568–575.
39. Milani-Nejad N, Trinidad J, Kaffenberger BH. Viral reactivation in hospitalized patients with drug reaction with eosinophilia and systemic symptoms: a retrospective study from a tertiary medical center in the United States. *J Am Acad Dermatol*. 2020;83(1):278–279.
40. Cho YT, Yang CW, Chen YC, et al. Comment on “Viral reactivation in hospitalized DRESS patients: a retrospective study from a tertiary medical center in the United States.” *J Am Acad Dermatol*. 2020;83(3):e209–e210.
41. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome. part II: management and therapeutics. *J Am Acad Dermatol*. 2013;68(5):709.e1–709.e9; quiz 718–720.