San Diego Society of Hematopathology

Case of the Quarter

Q1 - 2017 Answer

1. *Atypical T-cell Proliferation with angioimmunoblastic-like features*

2. *Relapse of lymphadenopathy*

   Development of new lymphadenopathy

3. *Systemic symptoms ?*

4. *Detection of TCR Gene rearrangement (Clonality)*

WHAT'S THE DIAGNOSIS ?

According to clinical informations and clonality I suggested at first a diagnosis of lymphoproliferative neoplasm such as PTCL NAS with angioimmunoblastic like features.

but

- **Either bone marrow biopsy and total body CT were negative**

- **What's about the performance status of patient ?**

Then,

the pathologist met

the patient !

1. The patient was affected by Epilepsy !

She started anticonvulsant therapy

1 month previously the lymph node biopsy was performed.

Therapy: Lamotrigine and Sertraline

2. She didn't communicate neither her disease and therapy to any physicians !

3. On the other hand, any physicians didn't ask her about her clinical history, diseases, as well as about drug therapy !

4. I informed the hemathologist about epilepsy and related therapy but he only answered me that chemotherapy won't had been in conflicy with anticonvulsant drugs !

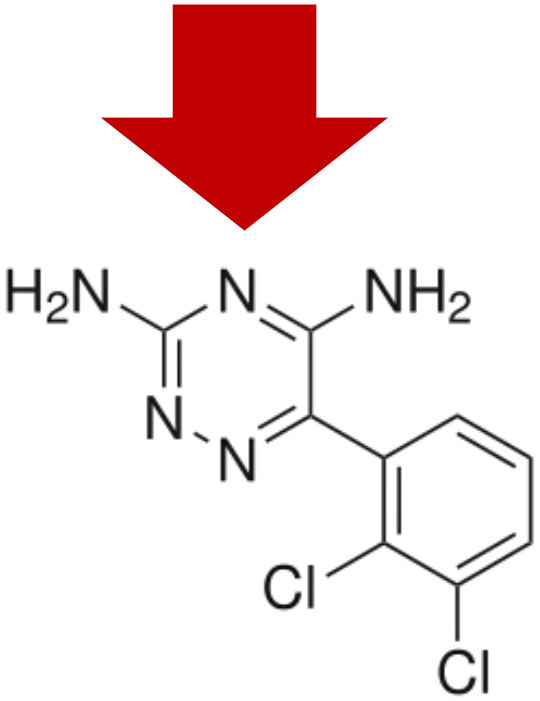
5. Do be careful:

clinicians often don't know the reactive lymphadenopaty in the setting of anticonvulsant drugs!

6. I didn't know the patient's clinical history about epilepsy and related therapy when I signed the diagnosis of PTCL at first time !

- **Sertraline** (a selective serotonin reuptake inhibitor)

- **Lamotrigine** (sodium channel blocking class of antiepileptic drugs)



- anticonvulsant drugs
- neuroleptics
- antidepressants drugs
- antibiotics

Lamotrigine's chemical structure contains an aromatic ring and is similar to phenytoin, carbamazepine and phenobarbital.

Lymphadenopathy Secondary to Lamotrigine (Lamictal®)

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ABSTRACT: We report lymphadenopathy in a 5-yo-female most likely secondary to lamotrigine. Lamotrigine is effective in the treatment of partial and generalized seizure disorders and often prescribed by neurologists and pediatricians because of its effectiveness in children with idiopathic, resistant generalized seizure disorders; it lacks cognitive impairment. Lamotrigine's chemical structure contains an aromatic ring and is similar to phenytoin, carbamazepine and phenobarbital. The patient had a documented drug allergy to both phenytoin and carbamazepine, and clinically improved following discontinuation of the lamotrigine. Clinicians should be aware of this potential adverse event for patients treated with lamotrigine.

Vet Human Toxicol 44 (5) October 2002

Lymphadenopathy is found among people who take **Sertraline** hydrochloride, especially for people who are female, 40-49 old, also take medication Ultram, and have Pain.

We study 10,745 people who have side effects while taking Sertraline hydrochloride from FDA and social media. Among them, 45 have Lymphadenopathy.

FDA

Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically pathologically malignant lymphomas.

SALTZSTEIN SL, ACKERMAN LV.

Cancer. 1959 Jan-Feb;12(1):164-82.

The American Journal of Surgical Pathology 19(6): 675–686, 1995

Dilantin-Associated Lymphadenopathy

Spectrum of Histopathologic Patterns

Susan L. Abbondanzo, M.D., Nelson S. Irey, M.D., and Glauco Frizzera, M.D.

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Case Report

Phenytoin-Associated Lymphoadenopathy Mimicking a Peripheral T-cell Lymphoma

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Abstract

We report a case of phenytoin-induced pseudolymphoma in a 28-year-old male with a history of autism and seizure disorder. The patient presented with bilateral cervical lymphadenopathy that was shown to be moderately to markedly FDG-avid on a whole body PET/CT scan. Flow cytometry analysis of peripheral blood and bone marrow mononuclear cells detected identical T cell population with aberrant immunophenotype. Additionally, a TCR beta gene was found to be clonally rearranged in both peripheral blood and bone marrow supporting a clonal origin of atypical T cells. However, no such clonal population of T-cells could be detected in a pathologic specimen obtained from an excisional biopsy of one of the patient's cervical lymph nodes. After discontinuing the patient's phenytoin, his lymphadenopathy has nearly completely resolved and circulation clonal T cell populatio disappeared with 12 months of follow-up.

- Angioimmunoblastic lymphadenopathy in a patient taking diphenylhydantoin.
  T sung SH, Lin JI. Ann Clin Lab Sci. 1981 Nov-Dec;11(6):542-5.

- **Immunoblastic lymphadenopathy occurring during treatment with carbamazepine. 2 cases.** Gouet D, Rouffineau J, Pouget-Abadie JF, Besson I, Becq-Giraudon B. Rev Med Interne. 1984 Mar;5(1):72-4.
  We report on two cases of dysimmune lymphadenopathies with histological aspect of angio immunoblastic lymphadenopathy (AIL) developing after administration of carbamazepine. Lymph node biopsy disclosed the angioimmunoblastic proliferation characteristic of AIL. After discontinuing carbamazepine, a complete remission was obtained.

- **Lymphoproliferative disorders associated with carbamazepine.** Katzin WE[1], Julius CJ, Tubbs RR, McHenry MC. Arch Pathol Lab Med. 1990 Dec;114(12):1244-8.

- **Carbamazepine**-induced **lymphadenopathy** mimicking Ki-1 (CD30+) T-cell lymphoma.
  Yeo W, Chow J, Wong N, Chan AT, Johnson PJ. Pathology. 1997 Feb;29(1):64-6.

- A case of **carbamazepine**-induced l**ymphadenopathy** resembling Kikuchi disease.
  Ganga A, Corda D, Gallo Carrabba G, Cossu S, Massarelli G, Eur Neurol. 1998;39(4):247-8.

- **Phenytoin**-associated lymphoadenopathy mimicking a peripheral T-cell lymphoma. Johns ME, Moscinski LC, Sokol L. Mediterr J Hematol Infect Dis. 2010 Sep 7;2(2

- Granulomatous **lymphadenopathy** secondary to **phenytoin** therapy.
  Ovallath S, Remya RK, Kumar C, Nayanar S. Seizure. 2013 Apr;22(3):240-1

- **Various medications may develop generalized drug-reaction lymphadenopathy that clinically resemble PTCL or AITL.**
- **Histologically, paracortical expansion of the lymph node by a polymorphous infiltrate including many eosinophils also can resemble AITL.**
- **Rarely, PCR studies can shows monoclonal TCR gene rearrangement in drug reactions as well.**
- **Lack of an aberrant T-cell immunophenotype is clue against a diagnosis of AITL.**
- **Of course, knowledge of recent drug administration is extremely helpful.**
- **Follow up often shows regression of lymphadenopathy in 1 to 3 months.**

(IOACHIM'S LYMPH NODE PATHOLOGY 2009 pag. 50)

A: DRESS Syndrome (severe adverse drug-induced reaction) hallmark features: **(1) fever (2) Adverse Skin reaction**, rash "pseudolymphoma sindrome" **(3) eosinophilia (4) multiorgan involvement (5) Lymphadenopathy (develop shortly after starting the drug)**

Drug Therapy (anticonvulsant)

(AHS) Anticonvulsant hypersensitivity Syndrome

B: Lymphadenopathy may develop as localized disease over a long period of time after onset of therapy*

Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) in an Adolescent Treated With Lamotrigine.

Ginory A[1], Chaney-Catchpole M, Demetree JM, Mayol Sabatier LM, Nguyen M. J Pediatr Pharmacol Ther. 2013 Jul;18(3):236-40.

Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a hypersensitivity syndrome most commonly associated with antiepileptic agents, allopurinol, and sulfonamides. It is a **severe adverse reaction** associated with **fever, rash, eosinophilia, lymphadenopathy, and internal organ involvement.**

We present the case of a 17-year-old Caucasian female with bipolar disorder type II and posttraumatic stress disorder treated withlamotrigine for a non-Food and Drug Administration-approved indication that developed DRESS syndrome at an initial dose higher than that recommended.

Her symptoms were atypical in that she developed a rash with influenza-like symptoms that resolved after discontinuation oflamotrigine and returned 8 days later. She was hospitalized because of elevated liver enzymes and treated with corticosteroids. In patients presenting with rash and systemic symptoms, DRESS syndrome should be considered and treated appropriately to reduce **mortality, which can be as high as 10%.**

Treatment includes withdrawal of the offending agent and corticosteroids.

Lymphadenopathy in the setting of Anticonvulsant Therapy

Histopathologig findings:

- **Paracortical proliferation of immunoblasts** (clusters or sheets) **atypical immunoblastic hyperplasia** resembling DLBCL; Reed-Sternberg-like cells may be also identified
- In some cases, **the degree of vascular proliferation, paracortical expansion, heterogeneous cellularity, atypical T-cell zone hyperplasia can resemble PTCL or AITL**
- **Reactive Follicles**. In lymphadenopathies that occur late after onset of therapy: **Lymphoid follicles may be atrophic disrupt or absent**
- eosinophils; histiocytes, plasma cells; neutrophils
- Necrosis/vasculitis: uncommon

"Atypical" Lymphoid Proliferation Associated with Medications and Therapies

- Autoimmune, inflammatory diseases
- Lupus, RA
- Immunomodulatory agents
- Methotrexate
- Monoclonal antibody anti-TNF
- EBV related (40%)
- Anticonvulsant-associated lymphadenopathy*

my final pathology report:

Nodal parenchima effaced by an atypical and clonal T-cell proliferation (CD4>>CD8).
According to clinical history (clinical data may be related to nodal proliferations with angioimmunoblastic-like features) and staging I cannot render a conclusive evidence for a diagnosis of PTCL until proven otherwise.
Finally, I favor a diagnosis of anticonvulsant drug- related reactive lymphadenopathy.
Careful observation regarding the evolution of the clinical picture after drug withdrawal is highly recommended.

- **5 years follow-up of the patient revealed us that lymphadenopaty was self-healing after drugs withdrawal. Furthermore, patient is safely and healthy now with an optimal performamce status.**

REMARKS

- This case represent an extraordinary example of hypersensivity reaction and iatrogenic drug-induced lymphadenopathy occurring in a patient treated with anticonvulsant therapy.

- **Then, do be careful before rendering a diagnosis of peripheral T-cell lymphoma (PTCL) in the setting of anticonvulsant therapy !**

TAKE HOME MESSAGES

- **Anticonvulsant drug-related lymphadenopathy may induce atypical changes in lymph node that can simulate malignancy such as T-cell lymphoma**
- **Obtaining a careful medical history**
- **Type and duration of any medications**
- **Evaluation after drug withdrawal**