ΔΙΑΝΟΣΟΚΟΜΕΙΑΚΗ ΕΠΙΣΤΗΜΟΝΙΚΗ ΣΥΝΑΝΤΗΣΗ
ΤΗΣ Α' ΠΡΟΠΑΙΔΕΥΤΙΚΗΣ ΠΑΘΟΛΟΓΙΚΗΣ ΚΛΙΝΙΚΗΣ
ΚΑΙ ΣΥΝΕΡΓΑΖΟΜΕΝΩΝ ΚΛΙΝΙΚΩΝ

6η ΚΛΙΝΙΚΟ-ΠΑΘΟΛΟΓΟ-ΑΝΑΤΟΜΙΚΗ ΣΥΖΗΤΗΣΗ 2017-2018

Πέμπτη 26 Απριλίου 2018, Ώρα 1.00 μ.μ.,

Αμφιθέατρο «Φαίδων Φέσσας» Γενικού Νοσοκομείου Αθηνών «Λαϊκό»

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Ιατρική Σχολή - ΕΚΠΑ

Σύνοψη

- Άνδρας 48, Φιλιππινέζος, με ΣΔ, Αλκοόλ
- 4 μήνες πριν: στις Φιλιππίνες, νοσηλεία λόγω Διαβητικού Έλκους
- 3 μήνες πριν: αρθραλγίες, αρθρίτιδα ΑΡ ΠΧΚ
  - Μεθυλπρεδνιζολόνη, ΜΣΑΦ
- Παρούσα νόσος: έμετοι, διάρροια, σύγχυση, πυρετός
- Φυσική εξέταση: διάχυτη κοιλιακή ευαισθησία, οιδήματα, αποπροσανατολισμένος, ↓μυϊκής ισχύος, έλκος κνήμης
- ↑CRP, WBC, ουρία/κρεατ, LDH, ALP, ουρικό
- ↓αλβουμίνες, pH
- Απεικονιστικά: πολυορογονίτιδα, εντεροκολίτιδα, ασβέστωση αορτικής

Εύρημα οδηγός στη δδ

- Ηωσινόφιλα: 4.900 Κ/μl (φτ <500)
- **Hypereosinophilia** — Hypereosinophilia (HE) in the peripheral blood is defined as an absolute eosinophil count >1.500 cells/microL on two examinations separated in time by at least one month **and /or** pathologic confirmation of tissue HE infiltration.
- **Hypereosinophilic syndrome** — A hypereosinophilic syndrome (HES) is defined by the association of HE (as defined above), with eosinophil-mediated organ damage and/or dysfunction
  - ΓΕΣ, ΚΝΣ, πνεύμονες, δέρμα, καρδιά, αρθρώσεις

ΠΦ υπερ-ηωσινοφιλίας

- Κλωνικός πολλαπλασιασμός λόγω μετάλλαξης
  - **Primary (or neoplastic) HES** – In primary HES, eosinophilic expansion occurs in the setting of an underlying stem cell, myeloid, or eosinophilic neoplasm, and is considered (or proven) clonal.
- Υπερπαραγωγή IL-5 (πολυκλωνικός πολλαπλασιασμός)
  - **Secondary (or reactive) HES**
    - parasitic infections, certain solid tumors, and T cell lymphoma,
    - Lymphocytic variant HES (L-HES) is a subvariant in this category
- **Ιδιοπαθές HES** (70-80%)
  - the underlying cause of HE remains unknown despite thorough etiologic work-up.

Ιστική βλάβη από ηωσινόφιλα

- Release of toxic granule products (eg, major basic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, or eosinophil cationic protein) that can damage epithelial cells and nerves.
- Production of lipid mediators, such as sulfidopeptide leukotrienes and platelet activating factor, which mediate smooth muscle contraction and recruitment of inflammatory cells.
- Release of cytokines such as GM-CSF, transforming growth factors (TGF)-alpha and -beta, and interleukins, which may be involved in tissue remodeling and fibrosis.

Κλινική εικόνα

- A retrospective multicenter series of 188 patients reported the frequency of specific symptoms at presentation
  - Dermatologic (eg, rash) – 37 percent
  - Pulmonary (cough and breathlessness) – 25 percent
  - Gastrointestinal – 14 percent
  - Cardiac – 5 percent
    - Ηωσινοφιλική μυοκαρδίτιδα
  - Neurologic – 4 percent
  - Myosceletal

J Allergy Clin Immunol. 2009;124(6):1319.

Νευρολογικές εκδηλώσεις

- Cerebral thromboemboli can arise from intracardiac thrombi and manifest as embolic strokes or transient ischemic episodes.
- Encephalopathy can present with behavioral changes, confusion, ataxia, and memory loss. Affected patients may also have signs of upper motor neuron injury, such as increased muscle tone, heightened deep tendon reflexes, and a positive Babinski response.
- Peripheral neuropathy accounts for approximately one-half of the neurologic manifestations of HES. The neuropathy may be symmetric or asymmetric, involve sensory with or without motor nerves, and may produce mononeuritis multiplex or radiculopathy with denervation muscle atrophy

Μηνιγγίτιδα

- Οσφυονωτιαία παρακέντηση: 10 κύτταρα (λεμφοκύτταρα), λεύκωμα: 109 mg/dl και λόγος γλυκόζης ΕΝΥ/ορού: 43/123 mg/dl.
- Καλλιέργειες ΕΝΥ για κοινά μικρόβια, PCR για TBC και ιολογικός έλεγχος ήταν αρνητικά.
- Έγινε έναρξη αγωγής με ριφαμπικίνη, ισονιαζίδη και πρεδνιζολόνη 25 mg x 2 iv με σταδιακή μείωση της δόσης της τελευταίας.
- Ελαφρά βελτίωση
- Ηωσινοφιλική μηνιγγίτιδα?
  - >10 eosinophils/mm^3 in the cerebrospinal fluid (CSF) and/or eosinophils accounting for >10 percent of CSF leukocytes.

ΓΕΣ

- Eosinophilic gastritis, enteritis, and/or colitis may occur secondary to HES and cause weight loss, abdominal pain, vomiting, and/or severe diarrhea
- Hepatic involvement
- Τη 10η ημέρα νοσηλείας διενεργήθηκε κολοσκόπηση που ανέδειξε εστιακή υπεραιμία βλεννογόνου σιγμοειδούς και εγκαρσίου. Οι βιοψίες ανέδειξαν βλεννογόνο παχέος εντέρου με οίδημα και ήπια αύξηση των χρόνιων φλεγμονωδών στοιχείων στο υπόστρωμα με συμμετοχή ηωσινοφίλων και λίγων ουδερετεροφίλων
- AST: 40 U/l, ALT: 31 U/l, γ-GT: 42 U/l, LDH: **604** U/l (φ.τ.: 135-225), ALP: **562** U/l (φ.τ.: 40-129)

Ηλ/κες διαταραχες λόγω διαρροικού

- ουρία: **71** mg/dl, κρεατινίνη: **1.70** mg/dl, Να: **122** mmol/l, Κ: **3.3** mmol/l, Ca: **6.7** mg/dl,
- pH: **7.26**, pCO2: 32 mmHg, pO2: **28** mmHg, HCO3: **14.4** mmol/l, SatO2: **42%**.
- Αλβ: **37.36%**, α1: **5.84**%, α2: 8.42%, β: 8.86%, γ: **39.52**%.

Μυοσκελετικο

- Αρθρίτιδα
- Ηωσινοφιλική μυοσίτιδα

Αίτια Υπερ-ηωσινοφιλικού συνδρόμου

Allergic diseases
Atopic and related diseases
Medication-related eosinophilias
Infectious diseases
Parasitic infections, mostly with helminths
Specific fungal infections
Other infections (infrequent)
Hematologic and neoplastic disorders
Hypereosinophilic syndromes
Leukemia
Lymphomas
Tumor-associated
Mastocytosis

Diseases with specific organ involvement
Skin and subcutaneous diseases
Pulmonary diseases
Gastrointestinal diseases
Neurologic diseases
Rheumatologic diseases
Cardiac diseases
Renal diseases
Immunologic reactions
Specific immune deficiency diseases
Transplant rejection

Λοιμώξεις

- Παράσιτα
- Μύκητες
  - Ασπέργιλλος
- Ιοί
  - HTLV-1
  - HIV

Helminthic parasitic diseases causing marked eosinophilia (>3000/microL)

Parasite	Notes
Angiostrongyliasis costaricensis	
Ascariasis	Early transpulmonary larval migration, often absent when mature
Hookworm infection	Early transpulmonary larval migration, often mild when mature
Strongyloidiasis	
Trichinellosis	
Visceral larva migrans	Primarily in children
Gnathostomiasis	
Filariases:	
Tropical pulmonary eosinophilia	Especially in expatriates
Loiasis	
Onchocerciasis	
Flukes:	
Schistosomiasis	During early infection in nonimmunes (Katayama fever)
Fascioliasis	During early infection
Clonorchiasis	During early infection
Paragonimiasis	During early infection
Fasciolopsiasis	During early infection

Strongyloidiasis

- *Strongyloides stercoralis* is endemic worldwide in areas with a hot, humid climate
- can directly penetrate the skin upon contact with soil or water contaminated with human feces.
- Strongyloidiasis can have a latency of years between the initial exposure and the development of symptoms, and infection easily could be overlooked if the patient or clinician were unaware of the possibility of remote exposure.

Toxocariasis

- *Toxocara canis* and *cati* are endemic worldwide and can be ingested with soil or food contaminated by dog or cat feces.
- This is typically a concern with children who may ingest contaminated soil.
- Affected individuals are acutely ill.

Trichinellosis

- *Trichinella* species have been reported worldwide.
- Human infections are seen most commonly in China, Thailand, Mexico, Argentina, Bolivia, and parts of Eastern and Central Europe.
- Infection results from ingestion of undercooked meat, especially pork.
- Testing by serology may be appropriate in individuals with potential exposure.

Hookworm

- *Ancylostoma duodenale* is found in Mediterranean countries, Iran, India, Pakistan, and Asia.
- *Necator americanus* lives in North America, South America, Central Africa, Indonesia, the South Pacific, and parts of India.
- These worms infect humans by larval penetration into skin.
- Affected individuals may have rash, cough, and gastrointestinal symptoms.
- Testing by stool studies is indicated in individuals with an appropriate exposure history.

Other parasites

- **Filariasis** – Filarial infections of humans can affect many different organs, including the skin, lymphatics, lungs, and eyes. Transmission is via arthropod vectors (eg, mosquitoes, blackflies).
- **Schistosomiasis** – Schistosome species are endemic in some regions of the tropics and Africa.
- **Protozoal parasites:** intestinal protozoa *Isospora belli*, *Dientamoeba fragilis*, and *Sarcocystis* species, which can cause peripheral eosinophilia. *Sarcocystis* can also cause eosinophilic myositis

Pros - cons

- Καταγωγή από ενδημική περιοχή
- Πρόσφατο ταξίδι σε ενδημική περιοχή
- Μη ανταπόκριση του συνδρόμου στα κορτικοειδή
- Προεξάρχει το γαστρεντερικό

- Κατά: αρνητικές παρασιτολογικές
- Ορολογικός έλεγχος: στρογγυλοειδές, κλπ ελλείπει

Αλλεργικές καταστάσεις

- Άσθμα
- Αλλεργική ρινίτιδα
- Φάρμακα

Φάρμακα που κάνουν ηωσινοφιλία

Manifestations	Commonly associated drugs
Asymptomatic	Penicillins, cephalosporins
Soft tissue swelling	GM-CSF, IL-2
Pulmonary infiltrates	NSAIDs
Interstitial nephritis	Semisynthetic penicillins, cephalosporins, NSAIDs
Myocarditis	Ranitidine
Hepatitis	Semisynthetic penicillins, tetracyclines
Hypersensitivity vasculitis	Allopurinol, phenytoin
Gastroenterocolitis	NSAIDs
Asthma, nasal polyps	Aspirin
Eosinophilia-myalgia syndrome	L-tryptophan contaminant
DRESS	Sulfasalazine, phenytoin, carbamazepine, allopurinol, hydrochlorothiazide, cyclosporine, nevirapine

Adrenal insufficiency

- Adrenal insufficiency has been associated with eosinophilia, especially in acutely ill patients. This is believed to be due to loss of endogenous glucocorticoids.
- Severe adrenal insufficiency presenting as isolated eosinophilia in an otherwise healthy individual is rare.
- In contrast, eosinophilia may be a marker of adrenal insufficiency in some high-risk settings (eg, tuberculosis, opportunistic infections in a patient with HIV infection, tapering or discontinuation of glucocorticoids, acute adrenal hemorrhage, necrosis, or infarction).
- In these settings, eosinophilia does not typically cause end-organ damage

Ρευματολογικές παθήσεις

- **Eosinophilic granulomatosis with polyangiitis** – (previously called Churg-Strauss syndrome) is the major vasculitis syndrome associated with eosinophilia. Patients typically present with asthma and other lung and upper airway findings; vasculitic symptoms typically develop years later
- Αντισώματα για κοιλιοκάκη και πλήρης ανοσολογικός έλεγχος (ANA, Anti-ENA, Anti-RNP, Anti- Sm, Anti –SSA, Anti-SSB, p-ANCA, c-ANCA, Anti-CCP, RF) ήταν αρνητικά.
- **Σαρκοείδωση**

Autoimmune lymphoproliferative syndrome (ALPS)

- Dysregulation of the immune system due to an inability to regulate lymphocyte homeostasis through the process of apoptosis
- The consequences of this include
  - lymphoproliferative disease, manifested by lymphadenopathy, hepatomegaly, splenomegaly, and an increased risk of lymphoma,
  - autoimmune disease,
- Patients with clinical features suggestive of autoimmune disease (eg, inflammatory arthritis) or immunodeficiency should have screening for ALPS (eg, enumeration of CD4 and CD8 double-negative T cells)

Toxin-induced syndromes

- **eosinophilia-myalgia syndrome**, attributed to ingestion of a contaminated preparation of L-tryptophan
- **Toxic oil syndrome**, caused by ingestion of edible oil adulterated with denatured rapeseed oil. Both of these entities are chronic, persistent, multisystem diseases.

Νεοπλάσματα

- Μυελικής σειράς
  - **Primary (or neoplastic) hypereosinophilic syndrome**
  - **Acute eosinophilic leukemia**
  - Chronic myeloid leukemia (CML)
  - **Systemic mastocytosis**
- Λεμφικής σειράς
  - **B cell lymphoma**
  - **T cell lymphoblastic lymphoma and adult T cell leukemia/lymphoma**
  - **Sézary syndrome**
  - **Precursor B cell acute lymphoblastic leukemia**
- Συμπαγείς όγκοι
- Ιδιοπαθές HES

Terminology for HES variants	Subtypes/identified abnormalities/examples	Clinical and laboratory features
Myeloid variants	*PDGFRB* and *FGFR1* rearrangements *JAK2* point mutation and translocation Chronic eosinophilic leukemia, not otherwise specified, on the basis of blast count in peripheral blood and/or bone marrow or of a clonal cytogenetic abnormality	↑ Serum B12 Anemia and/or thrombocytopenia Hepatomegaly and/or splenomegaly Circulating leukocyte precursors
	Deletion on 4q12 → *FIP1L1-PDGFRA* fusion	May show ↑ serum tryptase + mast cell abnormalities
		PDGFRA or PDGFRB rearrangement-associated disease occurs almost exclusively in males
T cell lymphocytic variants (L-HES)	Aberrant IL-5-producing T cells Example: CD3-CD4+ T cell-associated disease	Prominent skin findings (including plaques, erythroderma, urticaria) Polyclonal hypergammaglobulinemia Usually a benign lymphoproliferative disorder, but may progress to T cell lymphoma
Familial HES	Mapped to 5q 31-33	Asymptomatic eosinophilia from birth, autosomal dominant Progression to other forms of HES may occur
Idiopathic HES		Multisystem involvement with varied signs/symptoms
Organ-restricted HES	Examples include eosinophilic gastrointestinal disease, chronic eosinophilic pneumonia, and others	Peripheral blood eosinophilia associated with eosinophilic infiltration and associated signs/symptoms in a single organ
Specific/defined syndromes associated with hypereosinophilia	Examples include episodic angioedema with eosinophilia, eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss), other disorders associated with immune dysregulation	Marked eosinophilia in the setting of an underlying disorder associated with eosinophilia; the precise role of eosinophils in the disease manifestations remains uncertain

Διαγνωστική προσέγγιση Παρασιτικές λοιμώξεις

- Serologic testing for
  - **Strongyloides**. Positive serology in an untreated patient is presumptive evidence of infection
  - **Toxocara**
  - **Trichinella**
- **Stool studies** –stool testing for ova and parasites. The parasite eggs and/or larvae that may be identified in stool include Strongyloides, hookworm (ie, Ancylostoma duodenale, Necator americanus)

Διαγνωστική προσέγγιση Παρασιτικές λοιμώξεις

- Several helminths **cannot** be identified reliably by stool studies, including the following:
  - Strongyloides stercoralis
  - Schistosomes
  - Filariae
  - Trichinella
  - Toxocara species

Διαγνωστική προσέγγιση Νεοπλασματικά νοσήματα

- Μυελός των οστών
  - Νεοπλασματικά αιματολογικά νοσήματα
- Κυτταρομετρια ροής περιφερικού αίματος
  - Ανίχνευση παθολογικών κλώνων
    - including analyses for (at a minimum) CD3, CD4, and CD8 (to detect CD3 negative, CD4 positive subsets).
  - T cell receptor rearrangement studies on peripheral blood and/or bone marrow to diagnose lymphocytic variant HES.

Διαγνωστική προσέγγιση Νεοπλασματικά νοσήματα

- Bone marrow should undergo cytogenetic and/or specific molecular testing for hematologic neoplasms associated with eosinophilia, including the following:
  - Testing for chronic myeloid leukemia using cytogenetics, fluorescence in situ hybridization (FISH) for the t(9:22) translocation, or reverse transcriptase polymerase chain reaction (RT-PCR) for the BCR-ABL fusion product.
  - Testing for abnormalities of the platelet derived growth factor receptor (PDGFR) alpha or beta, fibroblast growth factor receptor 1 (FGFR1), and Fip1-like 1 (FIP1L1) genes.
  - Testing for PDGFRA-FIP1L1 is done using FISH for the CHIC2 locus and/or RT-PCR for the fusion transcript

Διαγνωστική προσέγγιση Νεοπλασματικά νοσήματα

- Serum B12 level (elevated in myeloproliferative neoplasms and autoimmune lymphoproliferative syndrome [ALPS])
- Τρυπτάση ορού
  - Σχετίζεται με νεοπλασίες της μυελικής σειράς

Πιθανές διαγνώσεις

- Παρασιτική νόσος με πιθανότερη το στρογγυλοειδές
- Πρωτοπαθές υπερ-ηωσινοφιλικό σύνδρομο
- Δευτεροπαθές υπερ-ηωσινοφιλικό σύνδρομο, οφειλόμενο σε
  - CD3-CD4+ T cell-associated disease

Ευχαριστώ