

A Case Of Lupus Related To Occupational Exposure?

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PGY1 Internal Medicine

Rheumatology Rounds

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Overview

- Case – (why AIMGP is great!)
- Common occupational and environmental exposures
 - Exposure route
 - Association with AI disease
 - Potential mechanism of action
- Practical implications

Mr. V

- **53 Caucasian ♂, North Simcoe Ontario**
- **Dec. 30, 2008: transferred from Huronia District Hospital to SMH NSx for “CN III palsy”, R. MCA aneurysm?**
- **PMHx: amblyopia with strabismus since childhood, 1990 - lumbar discectomy R. sciatica**
- **Medications: None. (including OTC, herbal)**
- **Previous smoker, 20 pack years, 10-12 EtOH/wk**

Mr. V continued

- **HPI: 7d Hx of progressive R ptosis**
- **Lateral (and vertical?) gaze palsy**
- **No other neurological symptoms**
- **Initial Phx: 101/65, HR 58, T 36.5,**
- **Chest “clear”, normal S1 & S2, abdo? MSK?**
- **Neuro: limited EOM (R. eye only), R ptosis – not fatiguable, no conjunctival injection or proptosis**
 - Sensation, power, reflexes unremarkable, no fatiguability, normal cerebellar and gait

Mr. V continued

- **Ix: Hgb 131, WBC 7.3, Plt 576**
- **Lytes N, Cr 75**
- **CT: no hemorrhage, infarct, mass, dissection. No aneurysm**
- **Initial dDx: ocular myasthenia gravis, nuclear R CN III palsy or infarct, R orbit pathology, thyroid disease, DM, HTN, CNS infection, vasculitis**

More about Mr. V

- **Admitted to neurology, multiple Ix**
- **EMG, trial of mestinon, lumbar puncture, TSH, CTA**
- **CRP: 65**
- **MRI: 1.5x1x1 cm pineal gland cystic/solid mass, non-compressive**
- **Metastatic workup: CXR and CT thorax – unilateral (LEFT) loculated pleural effusion**
- **Pleural fluid analysis: sterile, exudative (LDH) according to Light's criteria, -ve cytology**

And then...

- Improved on his own, discharged Jan 9
- Prior to discharge – vasculitic workup sent to be followed up in AIMGP clinic
- February 23rd - symptoms completely resolved, occasional headaches, not bothersome
- Phx: unremarkable except for decreased breath sounds (L) to 6th rib, rosacea

Mr. V

- **ANA +ve 19.9, anti-dsDNA ELISA 235**
- **ENA –ve, ANCAAs –ve, C3 1.9 g/L, C4 0.3g/L**
- **denied photosensitivity, malar or other rash, pleuritic chest pain, raynauds, hematologic condition, oral ulcers, arthritis/arthralgias, kidney disease**
- **No family history of autoimmune d/o**
- **ACR classification criteria for SLE: ANA, anti-dsDNA, serositis, neurologic involvement**

Social/Occupational History

- **Married, 3 healthy children**
- **Production manager for agricultural company - manufactures fertilizers and chemicals**
- **Is there a connection between presentation and occupational exposure?**

Occupational Exposures and Lupus

- **Recent epidemiologic studies suggest overestimation concordance of SLE amongst monozygotic twins in the past**
- **Increased prevalence of SLE in certain areas compared to national prevalence**
- **Exposures studied: silica, solvents, pesticides**

Crystalline Silica

- Sand, rock, soil; crystalline state = quartz
- Part of small particulate fraction of air pollution; sig. fraction of environmental dust levels in some geographic regions
- “dusty trades” china manufacturing, quarry work, masonry, mining
- Dental technician, chemist, sculptor
- Silica sand or flour: detergent filler; filtering agent for water, sewage, food production; 1^o component of abrasive cleaners (scouring powder)

Silica

- **Linked to AI since 1914 “unusual occurrence of scleroderma in stone masons”⁷**
- **Case reports and case series of stone masons and miners who developed scleroderma and RA**
- **Cooper *et al.* (2004)³ reviewed literature on occupational exposures and AI diseases**
- **Relative risk of 3.0 and higher observed for SLE and silica exposure**
- **Parks *et al.* (2002)⁶ case control study southeastern United States: dose response association. Medium exposure: Odds Risk 2, high exposure Odds Risk 4**

Silica

- **Inflammation and fibrosis of lungs and other organs**
- **Immune stimulant → increased production of proinflammatory cytokines TNF, IL-1**
- **Toxic to macrophages → apoptosis and increased exposure to intracellular self-antigens**
- **Brown and colleagues (2005)²: silica exacerbated disease development in lupus-prone mouse strain**
 - Increased autoantibody production, immune complexes, proteinuria, glomerulonephritis
 - Autoantibodies recognized apoptotic macrophages
- **Clearance mechanisms overwhelmed with silica containing macrophages transported to lymph nodes⁶**
 - Animal models of silicosis: ↑ Ig production result of accumulation of silica in lymph nodes
 - Intense exposures vs. cumulative life-time exposure

Solvents

- **Diverse collection of liquid compounds with different chemical properties**
 - Includes: alcohols, glycols, aromatic hydrocarbons, chlorinated products
 - Often used as degreasers or cleaners
 - Type vary greatly across workplaces
- **No association between solvents and SLE**
 - Two studies:
 - Tucson Arizona – high prevalence of ANA and SLE symptoms
 - Georgia - SLE
 - Animal studies: ↑ autoAb production when trichloroethylene added to drinking water
 - No studies in non lupus-prone mice⁷

Pesticides

- **Diverse group of compounds with variety of biologic properties and modes of action**
- **Classification:**
 - Function: herbicide, insecticide, fungicide, fumigant
 - Class: triazine, organophosphate, organochlorines
- **US and Canada:**
 - Herbicides: atrazine, glyphosate, acetochlor, 2,4-D
 - Fumigants: metam sodium, methyl bromide
 - Insecticide: malathion
- **Biologic measures of pesticides or metabolites (serum, urine) possible**
- **Only few studies examining relationship between pesticides and SLE**

Pesticides

- **Nogales Arizona: downwind and downriver from Nogales Sonora, Mexico¹**
 - Prevalence of SLE 103:100 000, 2-7x higher than U.S.
 - Case control study (19 cases) examining blood levels of pesticide metabolites
 - Elevated levels of 1,1-dichloro-2,2-bis-(p-chlorophenyl)ethylene and organophosphate metabolites among cases and controls
 - no significant difference between ↑ pesticides and disease state
- **Southeastern US: Mixing but not application of pesticides associated with SLE⁴**
- **Saskatchewan community based study: 2x ↑ prevalence of low titer ($\geq 1:40$) ANA with insecticide/herbicide exposure**
 - Association not seen in high titre ($\geq 1:160$)

Pesticides

- **Immunosuppressant effects and hypersensitivity effects:**
 - Organochlorine pesticides (OCP) and organophosphates
 - demonstrated immunosuppressive properties
 - enhanced production of immunoglobulins and autoantibodies
- **Endocrine-disruptors**
 - Effects on steroid hormones, gonadotropin hormones, thyroid hormone
 - Acceleration of disease development via estrogen-like effects
 - Sobel *et al.* (2005) demonstrated early appearance of ↑ anti-dsDNA antibodies and immune complex deposition in kidneys in ovariectomized lupus-prone mice treated with OCPs pesticides
 - Time course for development of auto-Ig comparable to effects produced by 17β-estradiol administration and non-ovariectomized controls
 - OCPs modify rate of progression but influence on incidence of disease unknown⁹

Summary and Issues

- Increasing interest in the role of occupational exposure in development of SLE
- Silica, solvents, pesticides
- Best evidence and most research into mechanism: silica
- Solvents, pesticides = broad categories, exposures not always known
- Experimental studies: lupus prone animals

Mr. V

- Committed to work
- Pesticides: organophosphates, others?
- April = busiest month, most exposure to chemicals
- Reluctant to take time off work
- Referral to occupational health at SMH and to rheumatology

Take Home Message?

- Literature raises questions but not convincing
- “incestuous” body of literature
- Small studies, cohort, case-control, case series
- Extend the rheumatologic history to include detailed exposure history?
- Referral to occupational health specialist?

Take Home Message!



References

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