Case Report

Microbiology & Infectious Diseases

Neuro Sarcoidosis Masquerading as Neuroborreliosis

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ABSTRACT

Background: *Medical syndromes often overlap in clinical presentations. Often there is one or more than underlying etiology responsible for the patient's Clinical presentation. We are reporting a patient who was initially admitted with fevers and joint pains.Lymes IGG was positive .He was discharged home on Doxycycline and Prednisone suspecting gout. Patient however was re admitted twice within 3 weeks with cognitive impairment. Lymph node biopsy was positive for non Caseating granulomas suggesting Sarcoidosis. Clinically he responded dramatically to steroids.*

Case Report: *74 year old white male was admitted with fever and multiple joint pains. Tmax was 100.5.WBC was 15 with normal CBC. LFTs were elevated .Rest of the labs were normal.Lymes IGG was positive. He underwent extensive Rheumatological and virological evaluation. Sonogram of the abdomen was negative. He responded to IV Ceftriaxone and was discharged home on Doxycycline for 3 weeks and Prednisone taper for a week .He was readmitted within 2 weeks with weakness and confusion. After ruling out multiple etiologies he was discharged home on IV Ceftriaxone suspecting Neuroborreliosis.But he was re admitted with worsening mentation in a week. This time he was diagnosed with Neurosarcoidosis with a lymph node biopsy. He responded dramatically to IV steroids, Methotrexate and one dose of Infliximab. Patient continues to follow up with the clinic and is now at his base line with no recurrence.*

Conclusion: *He is one patient where an underlying disabling pathology was missed twice. He is a case of chronic Lyme that was successfully treated to begin with. However he is also a case of Neurosarcoidosis Masquerading as Nueroborreliosis. Rarely is a clinical encounter so perplexing.*

This case also supports the existing literature that extended use of antibiotics for Lyme disease has no short term or long term benefits; instead it will put the patient at a risk of drug toxicity. From Palliative care evaluation in the hospital this gentleman is now back to his base line and is totally independent for activities of daily living.

Keywords

Lyme disease, Sarcoidosis, Neurosarcoidosis, Non Caseating Granulomas, Doxycycline, Cognitive impairment, Steroid Challenge and taper, Methotrexate, Lymph node biopsy, Borrelia burgdorferi (BB), ELISA (Enzyme link Immune Assay) and IFA (Immunofluorescence assay), Western blot (WB).

Introduction

74 year old white male patient was admitted in early August with multiple joint pains and fever. He had a history of Gout. Joints are painful for a month but got worse recently. He denied recent travel, trauma, medication changes, sick patient exposure and alcohol or drug abuse. He lives in the woods in a cabin and has two dogs. Several times he pulled off multiple ticks from his pets. His other past medical history was Coronary Artery disease with stenting, Hypertension and Asthma. In the emergency room his Tmax was 100. 5. Rest of the vitals were stable.

He was in moderate distress with pain. Right shoulder and Right elbow was tender to passive movements. Rest of the examination was normal otherwise. Admission WBC was 15000 with normal CBC otherwise. His Creatinine was 1.5 AST and ALT were 369 and 470 with a total bilirubin of 1.4 ALK was 138. Creatinine Kinase was 38. CRP was 4.5 with an ESR of 31. Right shoulder X ray showed severe Osteo arthritis and right elbow X ray showed moderated degenerative changes. Sonogram of the abdomen was negative. Lymes IGG was positive with negative IGM. IGG 18,30,39,41,45,58,66,93 were all positive. Ehrlichia and Babesia were negative Parvovirus IGG was elevated at 7 but IGM was negative. ANA and Rheumatoid factor were negative. Hepatitis serology, Urine Gonococcus and Chlamydia was negative. He was treated with IV Ceftriaxone 2 gm daily in house to which he did show good response. He was discharged home in 3 days on Po Doxycycline 100 mg twice a day for 3 weeks and a week Prednisone taper (suspicion of Gout).

Two weeks later patient was readmitted with generalized weakness and cognitive impairment. His short-term memory was significantly impaired. He was afebrile and hemodynamically stable. He was hardly able to recollect one in 3 things from his own past. His Attention span, Concentration and language were reasonable. He had a normal gait and no motor or sensory loss. WBC was 7.5 with normal CBC and CMP. His LFTs normalized this admission. TSH, B12 and Folic acid levels were normal. Urine was sterile. CT brain shows a nonspecific hypo density in the deep white matter which could be ischemic changes from Lyme disease (Figure 1). MRI suggested nonspecific flair on theT2 image which could suggest ischemic small vessel disease or chronic Lyme vs demyelinating lesions (Figures 2 and 3). A colorless CSF showed 20 WBC with 88% lymphocytes, Sugar 36 with 98 Protein. CSF VDRL was non-reactive and CSF Lymes was also non-reactive. CSF Cryptococcus was negative. EEG was negative for subclinical seizures. HSV PCR, Enterovirus PCR, VZV PCR, CMV PCR, EBV PCR (All on CSF), CSF cytology and Viral Encephalitis Antibody Panel was all negative. He was managed with IV Ceftriaxone 2 gm daily. A PICC line was placed and he was discharged home on this regimen with Outpatient follow up. His cognitive decline was stable at the time of discharge.

Within one week he was brought back with worsening confusion. No history of seizure activity at home. He was afebrile and hemodynamically stable at the time of discharge. Overall physical examination including motor, sensory and cranial nerve examination was intact. He was awake, alert and oriented to person. Speech was not grossly dysarthric. He was able to recognize gross objects but was not able to name its body parts. On three step commands, he was 0/3. Reading skills were normal. Writing skills were significantly impaired. He did know how to put a pen on the paper. He was unable to draw any components of the intersecting pentagon Or to try and write a simple sentence. On gait examination –He leaned to the right when he got out of the bed but he was able to catch himself. He needed Standby assist to mild assist to ambulate to the bathroom either with Examiner or his IV pole. His gait was mildly ataxic with normal base.

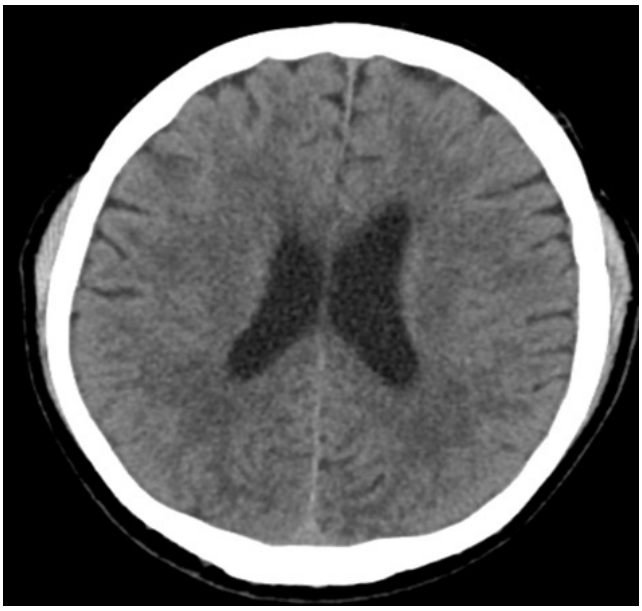


Figure 1: Nonspecific white mater changes.

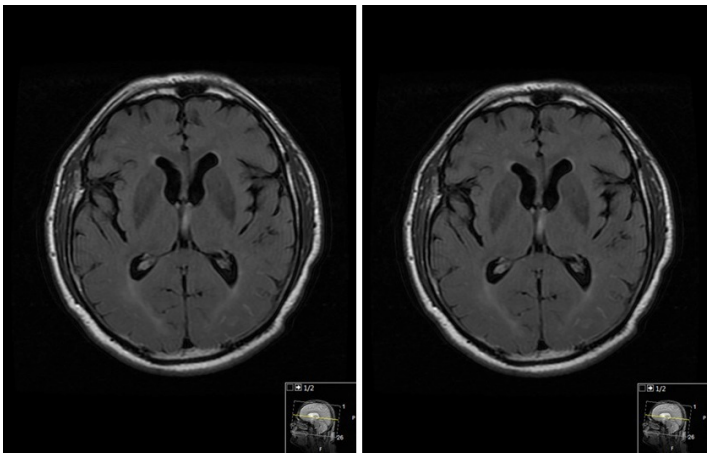


Figure 2: MRI brain FLAIR - nonspecific white matter T2 hyper intensity, most commonly seen with chronic small vessel disease but can be seen with sarcoid.

Figure 3: MRI FLAIR – abnormal leptomeningeal T2 hyper intensity.

Admission labs showed a WBC of 10. Rest of the CBC and Chemistry was normal. CRP was again elevated at 3. CSF showed a WBC of 65 with 96% lymphocytes. CSF glucose was 36 with a protein of 150. Cryptococcus was again negative. Chest X ray and Ct Brain was unremarkable compared to prior imaging. Given his

past history of smoking Paraneoplastic lesions were high on the diagnosis and he underwent CAT scan of the chest, Abdomen and Pelvis that showed Mild increase in size of axillary and mediastinal lymph nodes without lymphadenopathy (Figure 4). This by size criteria is nonspecific and is most probably reactive. They compared this to the CT chest done 2 years ago for a suspicion of pulmonary embolism. All along, his CSF cultures were negative including AFB and fungal cultures. Finally he underwent ultrasound guided core biopsy of the axillary lymph nodes (Figure 5). Tissue was negative for Acid fast bacilli and yeast (Figures 6 and 7). Pathology was positive for Non-Necrotizing Granulomatous Lymphadenitis consistent with Sarcoidosis (Figure 8).

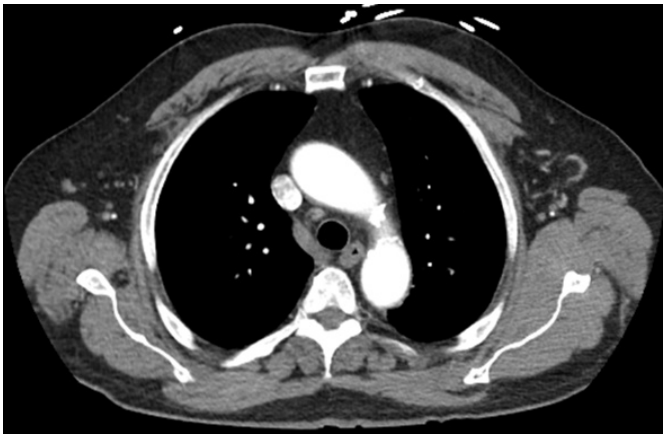


Figure 4: CT chest – mild left axillary adenopathy.

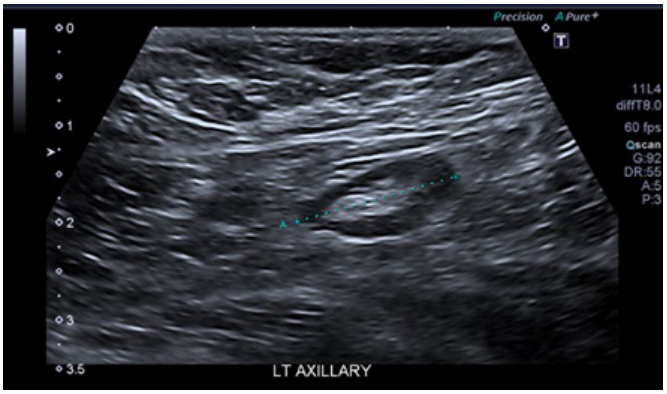


Figure 5: US biopsy – left axillary lymph nodes.

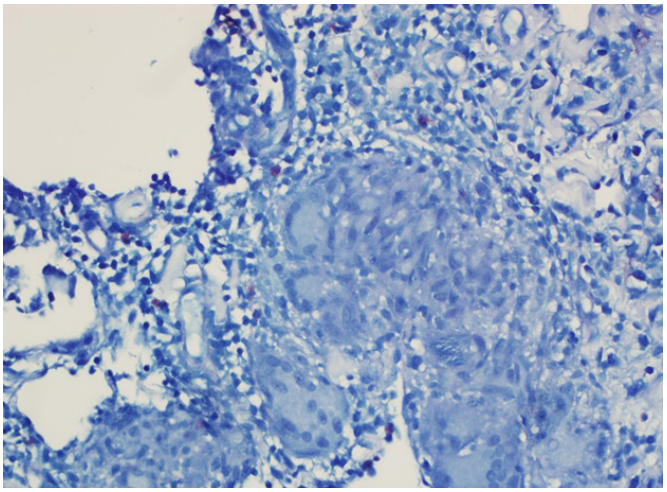


Figure 6: Negative AFB.

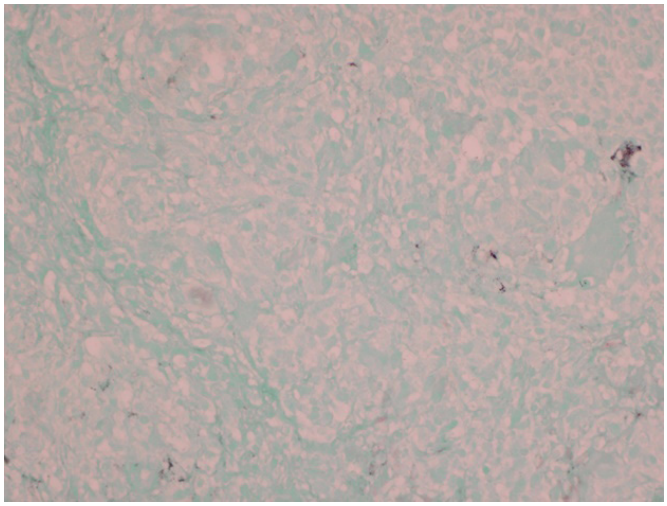


Figure 7: Negatvie GMS stain for yeast.

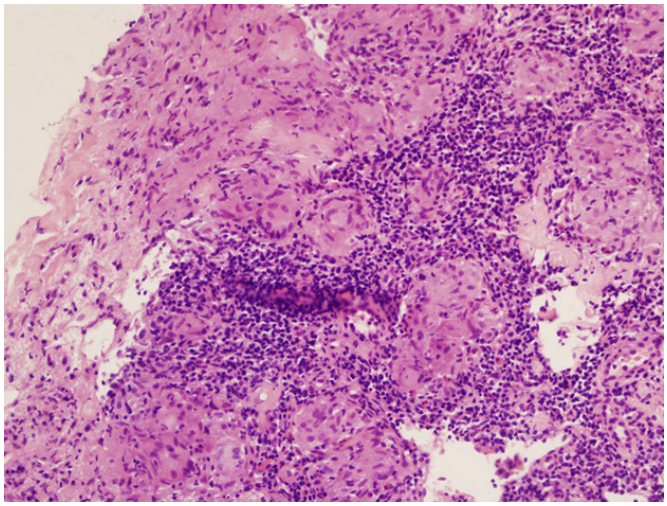


Figure 8: Non caseating granulomas.

By this time he was done with 28 days of IV ceftriaxone and also 2 weeks of Doxycycline. All antibiotics were stopped. He was challenged with IV Methylprednisolone 125 mg times one on day one and then he was given 80 mg on day 2 and day 3. Simultaneously Methotrexate 20 mg (MTX) weekly was also started. He slipped into steroid psychosis on IV Methylprednisolone and was managed with Baclofen and Alprazolam. He was then switched to Oral Prednisone. He was also given one dose of Infliximab. Patient showed dramatic improvement with this regimen. He was later discharged home on Po Prednisone. He continues to stay on Prednisone 10 mg daily and MTX 2.5 mg thrice weekly. He is now at his base line and is totally independent.

He was a case of Systemic and Neuro Sarcoidosis masquerading as NeuroBorreliosis. Repeat CSF sampled one month later showed normal WBC, normalized Glucose and Protein count. He definitely had chronic Lyme illness. Even If he had NB, he was more than adequately treated with only partial response.

Discussion

This is one case where we get to discuss two etiologies. Lyme disease and Neuro Sarcoidosis.

Lyme disease was first discovered in the Old Lyme County, Connecticut when there was an outbreak of Juvenile arthritis in 1977. This illness is caused by a spirochete BB. Ixodes Scapularis (the black legged tick) and Ixodes pacificus are the only two ticks known to transmit this spirochete. The former tick is seen in the North East and Midwest regions of the United States while the latter is mostly restricted to the North Pacific regions and Northern California. William Burgdorfer was the Swedish entomologist who first isolated this spirochete. This bacterium is not transmitted by other routes viz –sex, sharing linen or utensils or by other close contacts. This is seen in the donor blood of infected patients though. Annually nearly 300,000 new cases are diagnosed in the United States. Vertical transmission to fetus is also documented but to date this spirochete is not teratogenic like the syphilis agent. While BB is the only spirochete seen in the United States, Borrelia afzelii and B garinii are two other spirochetes seen in the Europe and rest of world in addition to BB. A novel pathogenic Borrelia burgdorferi sensu lato genospecies (candidatus Borrelia mayonii) in the upper Midwestern USA, which causes Lyme borreliosis with unusually high spirochaetaemia, has been described in the literature. Migratory birds are proven to carry the nymphs and adult vectors and help with widening of the BB territory. Squirrels are natural reservoirs for BB in the western United States. In the North eastern region white footed mouse, chipmunks and Voles are natural reservoirs. Nymphal activity is high in summer months and so is the incidence of Lyme illness. Borrelia bissettii is another spirochete in the United States and is not a human pathogen. Adult ticks feed on the white tailed deer but they are not natural reservoirs [1-8].

Ticks usually have four phases on their life cycle. Eggs, Larval stage, Nymphoid stage and the adults. All these stages need a bloody meal for their development. Nymphs and female adults are the usual vectors for the spirochetes. Ticks generally attach to the popliteal region, axillary region or the belt region of the body. It generally takes more than 24 hours for the tick to get attached to the body firmly. It takes another day or two puncture the skin and get engorged with human blood. Hence ticks attached for less than 72 hours and not engorged are usually not effective vectors. It usually takes 48 hours for the BB to migrate from the midgut to salivary glands of the tick. Bite is painless most of the times because of numbing agents in the tick saliva. Ones the spirochete is released in to the blood stream a target lesion usually develops but only after 24 hours. Skin lesions happening with in the first 24 hours of Tick contact is usually due to skin irritation from saliva and not Erythema migrans (EM) [9,10].

EM can happen any time 24 hours to a month after the tick bite. EM is generally a macular lesion that spreads over a period of few days with central healing. Often seen is the puncture site of inoculation at the center. This is generally painless with no vesicles or pustules. Presence of vesicles or pustules with pain should alert for other etiologies. This is the early localized phase of the disease and is usually associated with non-specific constitutional symptoms like fever, body aches, fatigue, arthralgias and regional lymphadenopathy. Visceromegaly doesn't happen in any stage of Lyme illness. Early localized illness is followed by spirochetemia, early disseminated disease where the bacteria literally spreads to every organ system in the body. As a spirochete, BB mimics another spirochete, Treponema pallidum. This phase occurs weeks to months after the tick bite and is characterized by multiple EMs and organ system manifestations l ike carditis, migratory arthralgias, uveitis, choroiditis, retinitis, localized or diffuse lymphadenopathy, hepatitis, microhematuria, meningitis, cranial and peripheral neuropathy etc. Multiple EM only suggests bacteremia and not multiple tick bites. Blood cultures are positive in less than 30% of the patients in this phase and are not commercially available. Positive Blood cultures are not necessary to establish a diagnosis of Lyme. Borrelial lymphocytoma is a skin condition seen in this stage but only in the European population [11].

Months to years after a tick bite the bacteria enters in to a latent phase evading the host immune system finally manifesting with a variety of systemic issues like Syphilis. Musculoskeletal, Neurological and Cutaneous system usually takes the brunt of this chronic pathogen infestation. Most of the times it will be a mono articular arthritis and knees are the most effected joints. Encephalomyelitis and peripheral neuropathy are the usual Neurological symptoms. Exclusively seen in the European population are two skin lesion called acrodermatitis chronica atrophicans, morphea/localized scleroderma. These two skin lesions are associated with cosmetic damage and with underlying neurovascular disruption [10-12].

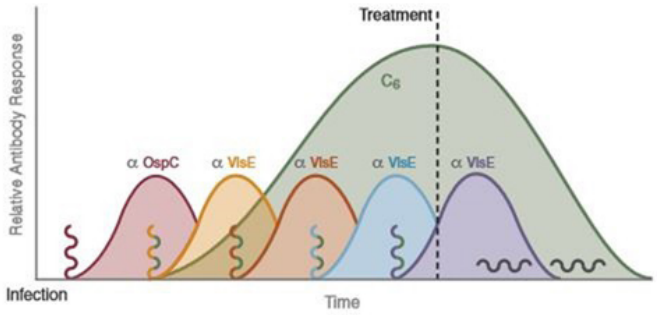
EM if present is enough to clinch the diagnosis of Lyme disease. Astute Infectious disease consultant s doesn't recommend any further serological studies if EM is seen at the initial presentation as long as the lesion did not appear within 24 hours of the tick bite. For all other cases there are only two serological studies offered. An initial screening test with the ELISA or IFA. If this is positive or equivocal with associated symptoms and clinical signs then we suggest proceeding with a final confirmatory western blot IGM and IGG test. This test basically recognizes the antibodies against various cell wall antigens in BB. If ELISA or IFA is negative then no further testing is warranted unless the serum sample was drawn very early in the onset of illness. If western blot is negative then patient doesn't have Lyme disease. Syphilis, Yaws, Pinta, Borrelia miyamotoi, Leptospira and Relapsing fever can all cause false positive antibodies on ELISA or IFA. 5% of normal population will test positive for Lyme because of cross reactivity to normal flora or other agents cited above. Previous Lyme vaccine can also cause positive test. Lupus, Rheumatoid arthritis, polyclonal B cell activation, EBV, Malaria, varicella are few other causes for positive Lyme ELISA. WB is a qualitative test and can pick up faint cross reactive bands from false positive sources. ELISA is a quantitative test. This is the reason why we perform WB only when ELISA is either positive or equivocal.

IGM antibodies appear in the first four weeks of infection and

unlike other infections can persist for years. IGG usually appears only after 4 weeks. If western blot is positive for 2 of the 3 IGM bands then it's a positive IGM WB test. If WB detects 5 of the 10 IGG bands then it's a positive IGG WB. If after 4 weeks of infection IGG WB is negative then this was a false positive IGM study. Lyme serologic testing yielded sensitivities in the range of 29–68% and specificities of 96-100%. Mean sensitivity was 56% and specificity 99%. Sensitivity of serologic testing is poor in early localized disease. Specificity was uniformly excellent in all disease settings at 99% [13,14].

BB evades the host immune system with efficient variations in its surface protein presentation. This is usually associated with mutations at the level of the genome. The resulting borrelial surface antigenic diversity impairs serodiagnostic performance especially by immunoblot. This aberration usually effects the IGM studies and not the western blot IGG studies.

To overcome this problem assays were developed against the C6 peptide that doesn't undergo any antigenic variation. This is an immunodominant, largely conserved 26-mer oligopeptide. This corresponds to the 6 th invariable region (IR6) with in the surface protein called the Vmp-like sequence, expressed (VlsE) protein. VlsE is a surface protein of B. burgdorferi. It is encoded by the VlsE gene. IR 6 region of VlsE is antigenically conserved across Lyme-related genospecies. The VlsE gene is only expressed in the mammalian host. The gene is not expressed when the organism is within the tick or when it is grown in culture to produce the Lyme vaccine. Therefore, antibodies generated as a result of Lyme vaccination do not react with the C6 peptide. Antibodies to the C6 peptide are an indication of natural infection with B. burgdorferi.



Active *B. burgdorferi* infections stimulate the C_6 antibody response.
At initial infection, a spirochete (ŝ) expresses OspC on its surface (red). With time, it must change the coat protein to evade the immune response (α OspC, red line). So by 10 days postinfection, the spirochete no longer expresses OspC and instead begins to express different VlsE coat proteins over time, each of which includes C_6. This drives C_6 antibody concentrations higher. Following treatment, the organism becomes dormant, no longer expresses VlsE and C_6 antibody concentrations decline.

C6 ELISA test is generally offered as a two tier test. ELISA to the whole cell lysate is run first followed by the C6 ELISA. In the setting of early disseminated phase acute neurologic or cardiac disease, C6 IgG performed equally well to combined standard IgM/IgG testing at 100% sensitivity and 96% specificity , but demonstrated increased sensitivity of 100% compared to use of the standard IgG alone with 85% sensitivity. Sensitivity of C6 testing remained poor comparable to standard testing in the setting of early localized disease at 29% in acute-phase EM, 56% in Convalescent-phase EM. To date all 3 standard tests have 100% sensitivity in late Lyme disease. Over all the positive predictive value and negative predictive value of these tests only make sense when applied with good history, clinical inspection of the patient and the location of occurrence of infection [14,15].

Like syphilis, Lyme borreliosis can cause Neuro borreliosis (NB) in 10-15% of the patients. However the presence of confusion in early or late Lyme doesn't establish a diagnosis of Lyme encephalopathy. This could be an altered sensorium usually seen with other infections too. Of the 30,000 new cases we see every year in the United States only 8% have facial nerve palsy which equals to 10 /100000 patients of which 25% are bilateral. Otherwise there is no good data on the incidence or prevalence of NB. In highly endemic regions facial palsy incidence can be as high as 24/100000 patients per year. Lymphocytic meningitis, Radiculopathy (Bannwarth syndrome), Peripheral neuropathy, Mononeuropathy multiplex, Cerebellar ataxia and Encephalomyelitis. Last two are very rare to see. The classic triad of acute neurologic abnormalities is meningitis, cranial neuropathy, and motor or sensory radiculoneuropathy. Headache, fatigue, insomnia, cognitive slowing and memory problems are all nonspecific findings only and don't support neuronal involvement. Facial nerve is the cranial nerve involved in 80% of the patients. Optic nerve, extraocular nerves and eight nerve involvement is also reported. Radiculoneuritis can occur in 3% of the patients who present with a neuropathic like pain. Brachial and sacral plexopathy is also documented in few patients. Demyelinating lesions with Lyme is still debated. Lyme meningitis is an aseptic picture with lymphocytic predominance. Very rarely can an organism be seen in meningitis. Encephalomyelitis usually mimics Multiple sclerosis in clinical presentations, CSF findings and on the imaging. Pediatric patients can develop benign intracranial hypertension. In cross-sectional studies of neuroborreliosis and unspecified Lyme borreliosis, the sensitivity was comparable to the case-control designs, but the specificity decreased to 78 and 77% respectively. Two-tiered tests did not outperform single tests. Specific antibody index tests did not outperform the other tests for NB. Serological testing on CSF or synovial fluid really adds no new information to the existing diagnosis and is not recommended. PCR testing is also not generally recommended. However CSF analysis clubbed with elevated albumin ratio indicating impaired brain barrier function and increases IGG and IGM index in the presence of oligo clonal IGG and IGM bands in CSF all complement for the diagnosis of NB. However these findings are not limited to NB [16-19].

Doxycycline 200 mg as a single dose is effective post exposure prophylaxis if given in an endemic region within 72 hours of an engorged tick bite. However this regimen has no beneficial effect in preventing other tick borne illnesses like Anaplasma, Babesia and Ehrilichisois. Penicillins and Cephalosporins are so far not evaluated in larger trials for post exposure prophylaxis [20]. BB is usually sensitive to Penicillins, cephalosporins and doxycycline. Oral treatment is usually effective with doxycycline for almost any stage of illness given the excellent oral bioavailability and

good tissue penetration of the drug. However IV Ceftriaxone is preferred in patients with meningitis, radiculitis, encephalitis, first degree heart block with PR interval greater than 300 milliseconds, second and third degree heart block, recurrent arthritis and arthritis with neurological manifestations. IGM and IGG antibodies can persist for several years to a life time and there is no need for a quantitative follow up. ESR and CRP will be more productive labs coupled with overall clinical progress. Treatment duration is anywhere from 2 to 4 weeks. Prolonged treatment beyond 4 weeks only adds up drug toxicity and carries no clinical benefits to the patient and the practioner. A sustained release form of doxycycline is proven to prevent Anaplasmosis in animal models [20-22.

To date there is no documented resistance of BB to any of the above mentioned agents. There is no proof of persistent infection with BB after successful completion of any regimen. However research has definitely proven that latent or dormant forms of the spirochetes are morphologically and physiologically different invitro from the actively dividing spirochetes and exhibit higher MICs for the above agents. Animal models have proven chronic persistence and resurgence of BB after completion of treatment. To date there is no evidence for this in vivo Post Lyme Syndrome is mostly a diagnosis of exclusion and extended use of antibiotics has no clinical significance. Besides the above mentioned screening tools there is no other diagnostic tool approved by FDA and there are no other alternate drug regimens either [23,24]. Prevention is by avoiding tick bites. The only vaccine available in the past is now with drawn from the market [25].

Sarcoidosis is a multisystemic autoimmune disorder of unknown etiology. A plethora of interactions between the host and the environmental agents are blamed to cause sarcoidosis (Figure 9).

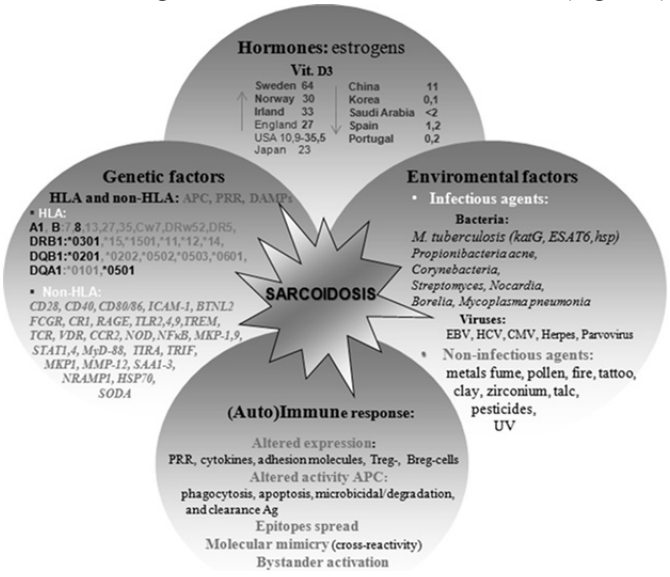


Figure 9: Etiopathology of Sarcoidosis.

While pulmonary system is the most commonly affected organ system any organ system can be involved and isolated cases of Neurosarcoidosis are well documented in literature. Like NB, Neuro sarcoidosis (NS) affects 10% of the patients with sarcoidosis. Females are more affected than males (6% vs 2%). Usual age of onset is in mid 30s. 30% of the cases progress to a chronic phase of illness. NS can be seen as a direct granulomatous inflammation of the nervous system or could be a neurological manifestation from systemic sarcoidosis or from the side effects of medications or from immune modulation [26]. Like NB can affect the meninges, parenchyma, ventricles, endocrine system, midbrain, cranial nerves and spinal cord all the way to the cauda equina, peripheral nerves and the myelin sheet. Clinical presentations include an aseptic meningitis picture which mimics a viral or syphilis or NB syndrome. Non caseating granulomas in the meninges will masquerade as a meningioma. Parenchymal involvement can be global or focal. Granulomas can present as intracranial mass in 30 to 50% of the patients. Encephalopathy, paresis or paralysis, seizures, gait and balance problems, chorieform movements etc. Involvement of the pituitary gland may present with primary problems like temperature dysregulation, SIADH and peripheral hormone imbalance manifestations from lack of stimulatory hormones from the pituitary gland (2-26%). Cranial nerve involvement is generally the V11 nerve like in NB. This can be unilateral, bilateral, simultaneous, consequent and recurrent. Any other cranial nerve can be involved but optic nerve and eight nerves are other common cranial nerves that can be affected. 4% of the patients develop throat, palate or vocal cord dysfunction. Peripheral neuropathy can be motor, sensory, autonomic, unilateral, and bilateral and recurrent. Caucasin population has higher incidence of peripheral neuropathy compared to the afro American population. Demyelination could be severe and manifest as Guillian-Barre syndrome. Hallucinations, depression, mood swings, dementia, apathy, fatigue, headaches and fevers could be non-specific symptoms from NS. A chronic non communicating hydrocephalus is seen in 5-30% of the patients and could be fatally progressive. Generalized or focal seizures are seen in around 15% of the patients. These two clinical presentations carry a poor prognosis [26,27].

Diagnosis of sarcoidosis is definitely on the histopathology with demonstration of non caseating granulomas. Other mimicking illnesses should be ruled out first. Diagnosis of NS is based on history, clinical examination, CT, MRI brain scan with gadolinium, Gal67 scintigraphy and FDG-PET. CSF examination is nonspecific but complimentary [28]. MRI is sensitive but not specific. Leptomeningeal enhancement is what we generally see on the MRI in 30-40% of the patients. Bilateral parotid and lacrimal glands uptake on scintigraphy and also in FDG-PET shows a characteristic “panda sign”. This sign is also seen in lymphoma and Tuberculosis. A combination of multiple fluorodeoxyglucose PET-avid lymph nodes with mild flurothymidine (FLT) PET uptake can be helpful in differentiating granulomatous inflammatory diseases like neurosarcoidosis from malignancy. FDG-PET and FLT-PET are more useful methods in localizing the optimum site for a biopsy than Gal67 scintigraphy and MRI [28-31]. Visually evoked potentials and auditory evoked potentials are non-invasive tests. They can be applied in NS involving the 2nd and 8 th nerve. They also help in quantitation of the disease progress [32]. Meningeal biopsy or brain biopsy is

of course the gold standard. Biopsy from any other involved tissue is also equally helpful. Electroneurography with low amplitude of muscle response –M wave is helpful in diagnosing the large fiber peripheral neuropathy. Granulomas are generally seen in the epineurium and perineurium. Endoneurium is usually spared. This has good prognosis compared to the small fiber neuropathy (SFN) associated with sensory and temperature disturbances and autonomic disturbances. A high risk of developing SFN is also associated with an increased frequency in the occurrence of HLA-DQB10602 antigen and/or non-HLA polymorphic genes encoded proinflammatory cytokines. Restless leg syndrome, paresthesias, burning pain or few symptoms associated with SFN. To diagnose SFN, skin biopsy with reduced intraepidermal nerve fiber density is essential in diagnosing SFN. Finally NS can affect muslces too. Granulomas are seen interspersed in the muscle fibers. Most of the patients are asymptomatic. Muscle weakness and atrophy is rarely seen. Elevated CPK elevated ACE levels and a myogenic pattern on Electromyogram is characteristic [26,27,33].

Corticosteroids are the drugs of choice for NS. We generally challenge the patient with Intravenous Methyl Prednisolone followed by a prolonged steroid taper for an indefinite period of time based on case by case basis. This regimen is generally recommended in severe NS with encephalopathy, weakness or vision loss. Steroid sparing agents include Methotrexate (MTX), Cyclophosphamide, Cyclosporine and Azathriopine. MTX is the first line agent in reducing steroid doses. Clinician should watch for drug toxicities from steroids and other alternative agents. MTX is myelo, nephro and hepatotoxic. It is teratogenic as well. Hepatitis, myelosuppression and pancreatitis are major side effects of Azathioprine. Cyclosporine is neuro and nephro toxic. Cyclophosphamide is myelotoxic and more worrisome is its teratogenicity and carcinogenicity. Mycophenolate mofetil is an analogue of MTX and can be used for NS but not in muscle NS. Chloroquine and Hydroxychloroquine are effective in NS and with sarcoid skin lesions. Tumor necrosis factor (TNF) blockers are also effective in helping with steroid taper and also with steroid resistant cases of NS. Infliximab, Thalidomide, and Adalimumab are the preferred agents. Infliximab is the second preferred agent after steroids. Major side effect of TNF blockers is increased risk of tuberculosis. Infliximab is the best agent for SFN. Hydrocephalus and psuedotumor cerebri will need surgery. Radiation therapy is proven effective in drug refractory cases. It will not help in total resolution of symptoms but will help with symptom reduction and disease stabilization. Patients with severe psychiatric symptoms, hemiparesis and extrapyramidal symptoms responded only to higher doses of radiation [27,34-36].

Conclusion

This gentleman definitely had chronic Lyme illness. He might have had NB too despite non conclusive extensive investigations. At that same time he did not have the typical clinical picture of sarcoidosis either. CNS evaluation was negative for any of the above mentioned clinical signs. The axillary lymph nodes were too small to be declared as lymphadenopathy in the first place. To biopsy such very small lymph nodes was a novel thinking on the part of the primary care providers. This patient was evaluated by palliative care team for end of life course. It was the biopsy report that changed everything. Lyme is a curable illness with the exception of Post Lyme syndrome which only needs symptomatic management. Sarcoidosis is a treatable illness often requiring life time immune suppression. Surgery is rarely needed in NS for hydrocephalus. Radiation therapy is one another novel angle in the management of NS.

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