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The Most Difficult Disease to Diagnose Even With Biopsy

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Sarcoidosis is granulomatous autoinflammatory autoimmune remitting relapsing disease affecting every organ in the body, it is the most difficult disease to diagnose in the absence of serum or imaging biomarker, Differential diagnosis is broad which included inflammatory, infective, neurodegenerative and neoplastic, histological biopsy is the only confirmative marker, and even histological confirmation is not robust as infection, malignancy and some drugs can induce granuloma, the most common organs affected are lung, lymph nodes, skin, eyes, liver, and less commonly pituitary gland, bones, brain, peripheral nerves, and heart, causing bilateral hilar lymphadenopathy, granulomatous lymphadenitis.

Lupus pernio and erythema nodosum, optic neuritis, granulomatous hepatitis, diabetes insipidus, periosteal bone erosion, pacchy and leptomeningitis, cardiomyopathy and conduction arrythmia respectively, two well scribed syndromes, the first one hereford syndrome which encompass granulomatous uveitis, parotid and submandibular lymphadenitis, and 7th nerve neuropathy, other cranial nerve might be involved, second syndrome is lofgren syndrome which comprise fever, arthritis, erythema nodsum, and hilar lymphadenopathy, prevalence of the disease is highest in western countries than asian and middle east population, it affects females more than males, the age of onset above 45 years up to 60, women can be affected at an elder age, sarcoidosis can be presented as subacute monofocal affecting one system or multifocal. Affecting few systems at the same time, mortality rate is greater than in general population if it affected the heart or brain, sarcoidosis can be remitting relapsing where patient will be fully asymptomatic after the relapse, or could be primary progressive where patient will never inter into complete remission after the first relapse or it could be secondary progressive where patients continue to have residual illness after each relapse.

Neurosarciodosis

Neurosarciodosis is a serious uncommon disease which could affect cranial nerves, meninges, brain parenchyma including pia matter and subarachnoid, it could also affect spinal cord and cauda equina, spinal vertebra, peripheral nerves and muscles, Neurosarciodosis had a very broad clinical manifestations which can masquerade as many other diseases like malignancy, infective, inflammatory or neurodegenerative in nature, Spontaneous remissions occur in about 50% of patients with neurosarcoid, all current practice stemmed from retrospective and autopsy series and from patients with systemic disease, that is why there is no guidelines about best approach for investigating, diagnosing and treating neurosarciodosis [1-4].

Cranial Neuropathy

Cranial neuropathy is the most common neurological manifestation of sarcoidosis, facial nerve is the most common to be affected, and it is commonly unilateral and less commonly bilateral.

In the most recent series optic neuritis started to be more common, bilateral optic neuritis can also occur, symptoms and signs included retro orbital pain specially with movement of the eye, blurring of vision, afferent pupillary defect, papilledema, decreased acuity of vision and impaired colour vision, field defects which included central, ventrocaudal and altitudinal, other cranial involvements are V111 nerve causing auditory and vestibular dysfunction, 111, V1 and V1 nerves can be affected in patients with involvement of leptomeninges causing compression of the cavernous sinus, olfactory nerve is rarly affected causing impaired taste and

anosmia, every patient should have MRI with gadolinium to look at enhancement of cranial nerve, compressive optic neuropathy my arise when disease affects the orbital apex and might cause hydrocephalus due to increased intracranial pressure.

CSF usually is bland or show increased protein, matched oligoclonal band is uncommon, sometimes CSF will show unmatched monoclonal band in isolated cranial neuropathy, isolated trigeminal involvement had been reported and posed a diagnostic problem in the presence of normal imaging and mildly active CSF with detection of unmatched oligoclonal band.

Isolated neuropathy of the lower cranial nerves is very uncommon but had been reported causing weakness and atrophy of one side of the tongue in addition to bulbar symptoms in the form of dysphonia and dysphagia, involvement of the lower cranial nerves occurs more commonly with basel meningitis rather than isolated cranial neuropathy, active CSF is common in Basel meningitis, with elevated protein, matched oligoclonal band and low CSF sugar with simultaneous serum sugar [5-7].

Pituitary and Hypothalamuses

Hypothalamic involvement is very common causing polydipsia and diabetes insipidus due to Subependymal granulomatous inflammation of the third ventricle, the two common manifestations are hyperprolactinemia and polydipsia due to diabetes insipidus, leptomeningeal inflammation and infiltration can cause mass lesion resulting in increased intracranial pressure, hydrocephalus, cerbellopontine angle lesion simulating neurofibromatosis type 11.

Neurosarciodosis should be in the differential diagnosis of seizures as it can cause seizure in up to 20% of patients with neurosarciodosis, which could be focal, generalized, focal with secondary generalization and even can turn into status epilepticus and occasionally non convulsive status epilepticus, due to leptomeningeal disease, parenchymal involvement, or metabolic disturbances due to hypothalamic involvement, usually CSF will be active with increased protein, lymphocytosis, low sugar and matched oligoclonal band, prognosis is poor in sever disease and patient might need to stay in life long anticonvulsant, steroid, immunosuppressive and biologic are indicated [8-11].

Peripheral Neuropathy

Peripheral neuropathy occurs in 10%-20% of patients, it can occur in isolation which caused a diagnostic Dilemma or concomitant with central neurosarciodosis, isolated peripheral neuropathy presents uncommon manifestation of neurosarcoid, diagnosis usually confirmed with histological diagnosis for non-caseating granuloma, symptoms are mainly sensory or sensomotor, sarcoid peripheral neuropathy could be small fiber neuropathy where nerve conduction study is normal, thermal threshold and cutaneous autonomic responses are subnormal in addition to intraepidermal nerve fiber density is reduced, in a series of 115 patients with small fiber neuropathy, 50% had cardiovascular instability, disorders of sweating, gastrointestinal delay as an autonomic complications, acute inflammatory demyelinating polyradiculopathy is uncommon, nerve conduction study showed multiple conduction blocks, normal motor action potential, biopsy usually showed granulomatous infiltration and usually patients are steroid responsive, and CSF is usually active,other types of peripheral neurosarciodosis are axonal neuropathy, chronic inflammatory demyelinating neuropathy, mononeuritis multiplex.

Mononeuropathy which is quite common specially for ulnar and radial nerves, Cranial neuropathy are more commonly encountered with Acute inflammatory demyelinating neuropathy and multifocal mononeuropathy despite that diagnosis is usually confirmed by granulomatous infiltration, not uncommon that necrotizing vasculitis or microvasculitis are encountered in the biopsy [12-19].

Pachymeningitis

Dural involvement is common in nerosarciodosis with predilection to Basel region and convexity, around 50% of patients with pachymeningitis will develop mass lesions causing seizures, common symptoms are headaches, orbital pain, diplopia, nausea, vomiting, reduced acuity of vision, impaired colored vision, visual field defect, cavernous sinus syndrome (pulsatile ophthalmopathy, third, fourth and sixth nerve palsy, encephalopathy) specially when the orbital apex is involved, patient may develop severe headache due to hydrocephalus, outcome is good if patient was timely diagnosed and received appropriate treatment (Steroid, immunosuppressive and biologic) Imaging is usually abnormal in all patients and CSF is active [20,21].

Leptomeningitis

Most patients have severe form of the disease in the form of meningoencephalitis, 50% of patients developed diencephalic dysfunction in the form of hydrocephalus and brain stem disease, patients with convexity Basel meningitis might develop cavernous sinus syndrome and encephalopathy, imaging is always abnormal, CSF protein correlates with the severity of hydrocephalus, patient should be treated with steroid, immunosuppressive and biologic, steroid alone is not optimum treatment.

Patients with leptomeningitis might develop large or small vessel stroke due to inflammatory involvement of small and medium vessel arteries causing stenosis of the vessels, of note patients with stroke due to leptomeningitis will not benefit from antiplatelet but will improve with steroids.

Focal stenosis of internal carotid, middle cerebral and anterior cerebral arteries might develop abnormalities resembling Moya Moya disease, few patients might develop subclinical disease with no symptoms patients with leptomeningitis might develop spontaneous intracranial bleed in a lobar distribution, infratentorial and even subarachnoid bleed needing urgent endovascular treatment. Few patients reported to have cortical vein thrombosis due to inflammation of the veins [21,22].

Spinal Cord

Involvement of the brain and spinal cord are common in leptomeningeal and Pachymeningeal disease. Isolated disease of

the spinal cord and cauda equina are also encountered, disease is usually subacute, extensive longitudinal disease of the spinal cord usually occur in leptomeningitis, smaller involvement of the cord occurs in pachymeningitis, most of the patients with lower dorsal spinal disease, will have involvement of the cauda equina, early sphincteric dysfunction and painless sensory loss is common in dorsal spinal disease and cauda equina involvement, in spinal disease with root involvement, patient will be manifested with amyotrophic signs which will be difficult to distinguish from motor neuron disease if sensation is intact but usually active CSF will be discriminating factor.

Patients with isolated neurosarcoid are still difficult to diagnose, Contrasted MRI, CSF and PET scan when imaging are negative, are essential investigation, histology and biopsy when possible is important for confirming the diagnosis, hypercalcemia and hypercalciuria are complementary if patient has subclinical systemic disease, reduced CSF and plasma CD8/CD4 ratio is supportive of the diagnosis.

Patients with isolated cranial disease has less active CSF than patients with systemic disease. 50% of patients with systemic sarcoid have elevated Angiotensin – Converting enzyme, it is nonspecific and found to be raised in other diseases like TB and cancer, Flucytometry from CSF and Plasma CD4/CD8 ratio is elevated, because of the absence of solid biomarkers to diagnose neurosarciodosis, neurosarciodosis diagnosis is classified to

1- Definite neurosarcoid if biopsy is positive (despite that malignancy and some infection can induce granuloma).

2- Probable neurosarcoid if investigation is supportive of the diagnosis, like elevated protein, presence of unmatched oligoclonal band, decreased SCF sugar with simultaneous serum sugar, Lymphocytosis, MRI with Contrast showing enhancement of inflamed areas, Evidence of systemic sarcoid, other criteria like ACE, chest X ray with bilateral hilar lymphadenopathy, Hypercalcemia, hypercalciuria.

3- Possible if above investigation are negative [23-25].

Differential Diagnosis

Differential diagnosis for neurosarcoidosis is wide and broad which included infection, inflammation, neoplastic and neurodegenerative diseases.

Neoplastic diseases, which included lymphoma (Steroid responsive) meningioma, metastatic carcinoma, neurofibromatosis type 11, glioblastoma, astrocytoma, glioma. Infections like mycobacterium TB, Mycobacterium Lepra, Brucellosis, Bartonella, Toxoplasmosis. Primary angiitis of the central nervous system, idiopathic hypertrophic pachymeningitis. Neuromyelitis Optica spectrum disorder, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), Sjogren syndrome, IGG-4 disease, Langerhans histiocytosis, Glial fibrillar acidic protein astrocytopathy, Erdheim -Chester disease. Collagen diseases, immune reconstitution syndrome, treatment with check point inhibitor for cancer [26].

Treatment

Steroid is the cornerstone of treatment, patient with leptomeningitis needs a high dose of steroid; most patients will need immunosuppressive, from series of Royal Free Hospital Dr Desmond P Kidd found that methotrexate 15-25 mg weekly is effective in his series, he also found that intravenous Cyclophosphamide is promising in sever disease despite the side effect which included serious infections but reduced relapse frequency.

Leptomeningeal disease is very serious and needs steroid, immunosuppressive and biologic treatment. Infliximab was found to be very effective in invasive leptomeningeal disease; patient should be screened for latent TB and hepatitis B before commencement of medication. Most literatures mentioned treatment should be continued for a minimum of two years. IL-6 blocker tocilizumab was used with success, Anti CD 20 rituximab showed promising results in few patients from the literatures [27-32].

Summary and Conclusion

One can never be 100% confidant of the diagnosis of neurosarcoid even with a brain biopsy as infection, malignancy and some drugs can induce granulomatous infection.

There is no one test or image to confirm the diagnosis but it might support. Diagnosis of systemic sarcoid is very supportive of neurosarcoid when it coexists. Neurosarcoid is a treatable disease if treatment is started in a timely manner. Patients should be treated with high dose steroid and immunosuppressive. Patients with invasive disease will need to be treated with steroid, immunosuppressive and biologic.

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