

MYSTERY OF MESENTERIC LYMPH ADENITIS

A ORIGINAL RESEARCH ARTICLE

Keywords:

Recurrent hyponatremia/ gastrocnemius muscle spasm (calf muscle cramps)/postural hypotension/giddiness/mesenteric lymphadenitis/Addison's disease/ Intestinal Tuberculosis/ Follicular Lymphoma.

A study to reveal the mystery on patients with above symptoms and signs to rule out infections or a complication of follicular lymphoma.

Abstract:

The etiological factors are confusing for provisional diagnosis and the differential diagnosis of mesenteric lymph adenitis; it may be virus like Dengue, Herpes and Epstein - Barr virus. Bacterial infections like Tuberculosis of the intestine through contaminated unpasteurized cattle milk or Mycobacterium tuberculosis through infected swallowed sputum. T. Gondii, Yesinia enterocolitica, pseudo tuberculosis infection. Lupus vulgaris in the face at the mucocutaneous junctions is a reactivation of already existing tuberculosis facilitates clinical diagnosis. Fungal infections like mucor mycosis, aspergillus, Fusarium producing neutropenia, Histoplasma capsulatum, Cryptococcus aerosol infection from droppings of pigeons on the AC machines. Kikuchi-Fujimoto's disease (KFD) . Autoimmune causative factors.

Introduction:

The above mentioned suspected etiological factors involve the self limited mesenteric lymph adenitis, turn out to be a histopathological diagnosis of follicular lymphoma is clearly in favour of KFD in the absence of neutrophils, absence of centralized caseating necrosis and granulomas with aggregates of

histiocytes with or without associated multinucleated giant epithelial cells to rule out Tuberculosis (1), (2). Viral etiology presents with vague clinical manifestations, lack of response to antibiotic therapy and certain histopathological features. Immune histochemistry the histological features and immune staining study of biopsy for differential diagnosis of abdominal tuberculosis, non Hodgkin's follicular lymphoma, lupus erythematosus and infections with other above mentioned etiological factors.

Concomitant non Hodgkin's follicular lymphoma post ATT therapy diagnosed as regression of mesenteric lymphadenitis resolved after chemotherapy (3). Nodular sclerosis in lymph nodes is the variant histopathological finding in mesenteric lymphadenitis. The pathogenesis hypothesized that Mycobacterium Tuberculosis causes direct DNA damage and apoptosis inhibition, which increases mutagenesis of progeny cells, combined with angiogenesis favoring tumor genesis. The mycobacterium cell wall produces nitric oxide and reactive oxygen species which induces mutagenesis. Nitrate DNA and oxidative DNA damage have been implicated in inflammation related carcinogenesis. Mantoux test reaction is low in the presence of malignancy, in the patients Mantoux highly reactive 23 mm positive and QuantiFERON test for TB released by CDC in Dec 2005 also positive indicates the pathogenesis of Tuberculosis. Rifamycin is a potent microsomal enzyme inducer especially cytochrome P-450 which induces enhanced metabolism of hormone cortisol and adrenal insufficiency (Addison's disease) with clinical symptoms of recurrent episodes of hyponatremia with clinical symptoms of recurrent calf muscle cramps, throbbing severe head ache, parasympathetic hyper peristalsis, high BP like 160/103 mm of Hg, giddiness, nausea, increased pulse at 90/minute. Treated symptomatically with slow IV of 3% sodium chloride to correct hyponatremia results in significant decrease in Hb percentage, platelets get reduced, WBCS reduced, change in coagulation profiles with uncontrolled bleeding followed by hemorrhagic shock. procalcitonin get increased from thyroid in inflammation or non inflammatory conditions like trauma, burns, surgery, severe cardiogenic shock, (normal 0.5 ng/ml to 2 ng/ml) make the Physician to rule out dengue. (4) Further analysis and investigation done by the authors to the patient like PET, ACTH stimulation test, ECHO, ECG,

several serological investigations and histopathology lymph node revealed the diagnostic criteria. Finally one good endocrinologist diagnosed it as Addison's disease, cortisol and Aldosterone insufficiency (primary with low cortisol and high ACTH), Whereas secondary adrenal insufficiency (low cortisol and low or normal ACTH), but to diagnose the etiological factor it may be autoimmune primary or secondary or tertiary. Due to mycobacterium Tuberculosis the pathology of adrenalitis and fibrosis may develop. Because cortisol is a glucocorticoid hormone synthesized from cholesterol by enzymes of the cytochrome P450 family in the zona fasciculata, the middle area of adrenal cortex, aldosterone deficiency seen in adrenal gland dysfunction with increased sodium loss and potassium reabsorption resulting in decreased intra cellular volume, vascular tone, cardiac output, and renal perfusion thus reduces arterial blood pressure leads on to postural hypotension, compensatory tachycardia, and vascular collapse. Reduced renal perfusion causes water retention, which dilutes the extracellular fluid and causes the cells to leak potassium, leads to hyperkalemia and metabolic acidosis. Circulatory collapse impairs urinary excretion of waste products, causing the elevated levels of blood urea nitrogen and creatinine. In Chronic steroid therapy by abruptly stopping their usual dose of corticosteroid 15 mg per day may manifest Addisonian crisis due to long term suppression of the hypothalamus pituitary axis. Tuberculosis on Rifamycin treatment produces cortisol insufficiency and precipitation of Addisonian crisis or Adrenal crisis is an acute deficiency of the adrenal hormone cortisol due to increased metabolism in the liver with clinical symptoms of throbbing head ache, metabolic encephalopathy, shock, breathlessness, abdominal pain and increased stools, tachycardia, hypertension, and giddiness. Emergency treatment with 100 mg hydrocortisone slow intravenous injection 4 hrly with follow up for 3 days or 20/10/10 mg hydrocortisone oral tablet relieve the symptoms and reduces the BP to normal. Constipation the next succeeding days a major problem treated with plenty of oral fluids and (Duphalac) lactulose non absorbable sugar syrup. On the 4th day oral hydrocortisone 10 mg in the morning, fludrocortisones 100 mcg or 50 mcg depends on Potassium low or normal, afternoon hydrocortisone 5 mg and night 5 mg. In physical or mental stress, severe head ache and calf muscle cramps the hydrocortisone dose to be doubled for 3 days and again maintenance dose. The

maintenance dose of hydrocortisone should not be below 15 mg per day. Fludrocortisone maintenance 50mcg per day. Monitor the early morning hypertension, it has to be corrected by stopping fludrocortisone or by amlodipine if necessary. After ATT therapy PET FDG shows mesenteric lymphadenitis may be due to non Hodgkin's follicular lymphoma or nodular sclerosis of mesenteric lymph nodes due to TB. It produces pressure effects on the blood vessels and causes ischemia, produce atrophy of adrenals and kidney to produce hydronephrosis or cyst in the kidney. Isoniazid 100 mg (INH) acts in disrupting the mycobacterium cell wall produces side effect as peripheral neuritis which is corrected with B6. Vitamin B6 Pyridoxine reduces cytokines in inflammatory chronic disease like Tuberculosis. Notalgia parasthetica is a sensory nerve compression in the spinal muscles at T2-7 clinically manifest as rash, pruritus in the interscapular region with recurrent pins and needle sensation treated with B12, B1, Magnesium tablets and supported by vibrator or low FD shock, Hot water bath and exercise. INH splits the fatty coating over the tubercle and liberates the mycobacterium. Rifamycin 600 mg bactericidal to the mycobacterium tuberculosis, treatment period is 9 months. Ethambutol 800mg acts by inhibiting the arabinosyl transferase enzyme and prevent arabinogelatin a mycobacterial cell wall constituent. Pyrazinamide 1500 mg induces pyrazinoic acid into the mycobacterium and prevents synthesis of fatty acid and disrupts the membrane potential treatment for 2 months. TB in association with HIV instead of rifamycin in ATT rifampin should be given. In addition Rifampin inhibits DNA Pox virus at concentration of 100 mcg/ml, but not on herpes. Rifampin on RNA virus Rous sarcoma virus inhibitory action established.

Haemological profile with mycobacterium tuberculosis which is siderophilic and depletes iron from the patient and ATT therapy rifamycin and INH causes haemolytic anaemia characterized by leukocytosis, thrombocytosis later leucopenia, thrombocytopenia and lymphopenia. WBC's shows occasional activated lymphocytes primitive myeloblast and lymphoblast with clefted nuclei are seen indicates inflammation and infection or neoplastic condition or haemolytic anaemia, this type of reactive leukocytosis are known as leukemoid reactions. Platelets show small clumps (indicates pseudothrombopenia due to the

anticoagulant used in the sampling test tube.) The presence of eosinophils and basophils in blood seen in combined adrenal insufficiency and inflammation (5) Anemia to be treated with iron and folic acid, vitamin C, protein and 3 to 4 litres of water minimize complications of drug toxicity of rifamycin like high grade fever, lassitude, weakness.

ECHO shows trivial regurgitation in mitral and tricuspid due to drug induced cardiomyopathy in association with anti tubercular drugs INH and Rifamycin. They are responsible for drug rash and eosinophilia, inflammation and myocytolysis resulting in myocardial necrosis and later fibrosis. Clinical symptoms of breathlessness, cough with whitish expectoration, generalized body swelling (peri orbital, parietal, and pedal). Raised JVP. Decreased oxygen saturation and later may go for heart failure. At that stage stop ATT and revive the patient with corticosteroids to control the paradoxical reaction and start levofloxacin and streptomycin after test dose to complete anti tuberculosis therapy. ECHO in some patients shows left ventricular global hypokinesia and left ventricular failure. Theory details of post mortum shows biopsy features of myocardial caseous necrosis and acid fast bacilli suggestive of tubercular myocardial necrosis. (6).

Positron emission tomography (PET) scan with 18 F- Flurodeoxyglucose tracer (FDG) the precautions before procedure are no strenuous exercise before 48 hrs, low carbohydrate diet, no sugar before 24hrs. 6 hrs before don't eat, take water only. Blood sugar should not be more than 200 mg/dl or 70 mg/dl. In this fdg will be concentrated faster in abnormal tissue than normal tissue. Stay warm one day before and on the day of procedure because special type of fat become active and absorb FDG and gives false report. Adequate pre hydration one liter of water to ensure a sufficient low concentration of FDG in the urine before 2 hrs then stop water. Wait for 45 mts for the FDG fluorine tracer to get absorbed. Urinate before going for PET-CT. 15 to 30 mts procedure of PET will be finished then take 3 liters of water per day to eliminate FDG radio active tracer from the body takes 12 hrs. From the myocardium FDG elimination takes 96 hrs. Fludeoxyglucose F 18 phosphorylated in the cell by an enzyme called hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphate.

FDG contraindicated in persons having glucose -6-phosphate deficiency . In

hypertriglyceridemia skeletal muscle FDG uptake (SMFU), myocardial glucose uptake (MGU) FDG absorption significantly reduced. Whole body insulin resistance the FDG uptake in myocardium and skeletal muscle reduced. PET usually takes 25 msv x-ray radiation, which is equal to 8 yrs of back ground radiation exposure. Hot spots of FDG in PET do not diagnose cancer, but they show abnormal uptake of the tracer. Cancer cells use lot of FDG and other diseases can produce Hot spots such as infection, inflammation. (100 msv exposure in PET is equal to 10000 chest X rays or 25 chest CTs.). Not more than 3 PETs can be done for diagnostic and prognostic values, this ionizing radiation dose and cancer risk takes a long duration of 10 years. Thus examinations should be clinically justified and measures should be taken to reduce the dose (7). Potassium acts as the counter ion of Fluorine to enhance its activity but does not interfere with the synthesis (8).

Differential diagnosis of lymphadenopathy the probable causes. Cryptococcus neoformans aerosol infection from droppings of pigeons on the AC machines is a life threatening infection. Lungs and CNS systems if infected, the other sites are optic nerve, bone, liver and lymph nodes. When disseminated presents as generalized lymphadenopathy, clinically mimicking tuberculous lymphadenitis. FNAC fungal isolation on culture with (DRBCm) Dichloran Rose-Bengal Chloramphenicol media reveals diagnosis. (9) Lymph node infarction associated with disseminated intra vascular coagulation in case of Dengue haemorrhagic RNA flavivirus(DENV). serotypes DEN 1 to 4 virus through Aedes aegypti and albopictus vector mosquito bit to human(10) Multiple sections of the infarcted or non infarcted lymph node failed to reveal any predisposing conditions. Lymphoma may coexist or follow lymph node infarction due to thrombotic occlusion in a case of previous Dengue infected serologically proven serum D – dimer , Dengue virus Ig M antibody ELISA positive. The infarcted lymph node on biopsy reveals variable positivity and the markers highlighted few reactive follicles. Drugs like Rifamycin, phenatoin show reactive changes in the lymph nodes. Maurer et al identified cases of malignant lymphoma synchronously with the infarct lymph node in Dengue on follow up turns to be malignant lymphoma in a lymph node infarct. However any infarcted lymph node due to Dengue should be eyed with suspicion

when it is enlarged in size(11). Past exposure to Dengue may provide some immunity against COVID-19 due to intriguing possibility of an immunological cross reactivity between the Dengue's Flavi virus serotypes and SARS-CoV-2. People with past Dengue fever history shows false positive for COVID-19 antibodies.

Chemotherapy with rituximab 375 mg/slow IV/ 15 days once and Bendamustine the chemotherapy drug 100mg in dilution/slow IV in 21 or 28 days interval for follicular lymphoma 5 to 6 doses regressed the mesenteric lymph nodes.

Rituximab on the first dose produce generalized urticaria, chest congestion, difficulty in breathing, bounding pulse or missed beats typical anaphylaxis to be treated as emergency. Rituximab is a monoclonal antibody, anti CD 20 on the surface antigen of the cancer cells and Bendamustine the chemotherapy drug gets concentrated on the cancer cells and act.

Abdominal distention after chemotherapy, long duration of antibiotics or steroids alter the intestinal motility, impaired Hydrogen gas handling, altered intestinal saprophyte bacteria and abnormal- phrenic nerve motor refluxes of dyssynergia for abdominal bloating and distension due to diaphragmatic contraction and decent and relaxation of the internal oblique muscle with gas load. Phrenic sensory nerve stimulation produces symptoms of gustatory rhinitis, usually come within minutes of eating with running nose, nasal congetion and sneezing treated with oxymetazoline hydrochloride drops one or two times because it produces atrophic rhinitis, if used habitually . Intestinal bloating, lower small bowl contraction when disaccharides of carbohydrate does not split to monosacchrides to get absorbed. Intestinal enzymes passes to large intestine the bacterial enzymes splits it into carbotic acids and gases which may cause irritable bowel syndrome or functional gastrointestinal disorder. In females the physiological intestinal bloating is related to menstrual cycle changes where estrogen is antibacterial, destroy the saprophytes and bloating in intestine occurs in progesterone period with hypersensitivity in the rectum (12). Gastrointestinal microbial saprophytes divided into two groups luminal saprophytes and intestinal mucosa associated saprophytes. Altered luminal flora like hydrogen consuming bacteria, for carbohydrate fermentation and production of hydrogen bloating in the intestine and abdomen. The low producer of methane by ingestion of sorbitol

and high fibers is destroyed by methanogenic flora. The luminal intestinal flora like non H_2O_2 producing lactobacilli, which facilitates the production of B complex and Vitamin K. Other organisms like bifidobacterium, vellionella, streptococcus, candida albicans. In large intestine 10^{11} organisms like E. Coli, bacteroids fragilis, streptococcus foecalis (enterococcus foecalis), pseudomonas aeruginosa, clostridium difficile in severe colitis. When saprophytes destroyed clinically it produces constipation followed by diarrhoea and abdominal colic due to higher levels of acetic acid, propionic acid and total organic acids. Treated with enterogermina having spores of polyantibiotic resistant bacillus clausii two billion in 5 ml suspension, nutrolin B plus capsule having lactobacilli four million spores, bifilac capsule containing streptococcus bacilli thirty million, clostridium butrycumbacilli two million.

RESULTS:

It is difficult to distinguish whether the extrapulmonary tuberculous mesenteric lymph adenitis is the first manifestation or follicular lymphoma or both to co-exists. In my study the Mantoux reaction was more in 40 % of 20 cutaneous Tuberculosis patients, where as the Mantoux negative with follicular lymphoma on follow up after ATT 20% is due to mitogenic effect of mycobacterium. PET CT scan reveals only concentration of the dye where there is inflammation. In 40% of patients both extrapulmonary mesenteric lymph adenitis and follicular lymphoma coexists. Due to Adrenal insufficiency in Tuberculosis and Follicular lymphoma 15 mg /day of Hydrocortisone in divided doses to be maintained by the patients.

DISCUSSION:

Recurrent hyponatremia clinically manifest as calf muscle cramps, giddiness due to postural hypotension treated symptomatically with 3% normal saline slow drip for 5 hrs. Then further investigations to be initiated for adrenal hypofunction and insufficiency of cortisol and aldosterone. The differential diagnosis of especially mycobacterium tuberculosis, its damage on adrenals and after effects of ATT the rifamycin and INH. The mycobacterium on the lymphnodes and its mitogenic

changes mimicking the pathology of non Hodgkin's follicular lymphoma and regression only after chemotherapy. Mantoux positive induration 23 mm confuses as if it is tuberculosis or associated concomitant follicular lymphoma, with cancer may show non reactive mantoux . Non Hodgkin's follicular lymphoma changes in lymphnode and no regression of lymph nodes after ATT therapy diagnosed histopathologically is a mystery for the physician to rule out follicular lymphoma.

CONCLUSION:

In recurrent hyponatremia, postural hypotention through investigations facilitates to early diagnosis and proper therapy to the patients. Mesenteric adenitis differential diagnosis and study on continuous related investigations with the cooperation of the patients and proper continuous therapy and iatrogenic side effects, combination of diseases and concomitant cancers diagnosed by hematology and pathology reports. The necessary chemotherapy promotes regression of the mesenteric lymph nodes proves the primary research on mycobacterium tuberculosis and its mitogenic effect on the lymph nodes. Rifamycin therapy in ATT induces leukemoid reactions and clefted nuclei confuses with blood related cancer.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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