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CLINICAL AND INVESTIGATIONAL PROFILE DIFFERENTIATING IMN FROM DIPHTHERIA

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ABSTRACT

Back ground: Diphtheria is an ongoing epidemic in the state of Kerala in India since 2016. Disease is characterized by fever, odynophagia and membrane in throat with or without adenopathy. We had a group of young immunized patients admitted with membranous tonsillitis with unique investigational profile. Based on this presentation, PCR and antibody testing of Infectious mononucleosis (IMN) was done and found positive. **Method:** Data was collected from the records of patients admitted with a clinical diagnosis of diphtheria in infectious diseases ward of our institution. When the clinical, biochemical and hematological profiles were found different from diphtheria, EBV PCR and Ig M viral capsid antigen (VCA) were sent. **Results:** We had 18 patients with proved IMN. All had history of full dose childhood vaccination. All these patients were young, had regional adenopathy bilaterally, membrane in throat, tonsillar enlargement, elevated total count, Lymphocyte predominance, peripheral smear showing large numbers of atypical Lymphocytes, low CRP, normal or slightly elevated ESR and elevated liver enzymes. None had splenomegaly clinically and USG wise. All had EBV PCR and Ig M VCA positivity. All Diphtheria patients had very high ESR and CRP, polymorphonuclear leucocytosis and normal liver enzymes. **Discussion:** Youngsters with membranous tonsillitis with lymphocytosis, predominant atypical lymphocytes in peripheral smear, low CRP and altered LFT may be screened for EBV, thereby we can avoid administration of costly antitoxin, antibiotic and prolonged hospital stay. Also atypical lymphocytes in peripheral smear, low CRP and altered liver function abnormalities can be taken as surrogate markers for diagnosis of IMN without going for costly investigations.

KEYWORDS: IMN, diphtheria, membranous tonsillitis.

INTRODUCTION

Exudative tonsillopharyngitis is a common disease which requires a careful clinical and laboratory assessment for identifying underlying etiology and proper management to avoid morbidity and mortality. The clinical symptoms include fever, dysphagia, odynophagia and pooling of saliva. Examination reveals pharyngeal congestion, erythematous uvula and soft palate and bilaterally enlarged tonsils covered with white/grey exudates which may coalesce to form membrane. Acute exudative tonsillitis involves a number of etiologic agents and a broad spectrum of severity depending on the etiology. The differential diagnosis for white or grey patch on tonsils includes streptococcal pharyngitis, diphtheria, infectious mononucleosis, candidal infection and anaerobic bacterial infection.

Pharyngitis due to Group A beta hemolytic Streptococci (GAS), the commonest etiology, is seen in older children and adults.[1] Fever, headache, and gastrointestinal symptoms (nausea, vomiting, abdominal pain) may also be associated with streptococcal pharyngitis. Physical examination reveals pharyngeal erythema, tonsillar enlargement, and a grey-white membrane covering the posterior pharynx and tonsillar pillars.[2] Petechiae are sometimes observed on the soft palate, with erythema and edema of the uvula. Anterior cervical lymphadenopathy is typical of GAS pharyngitis, and nodes may be large and tender. Tonsillar or pharyngeal exudates, tender anterior cervical nodes, fever or history of fever, and absence of cough are the signs and symptoms most indicative of GAS pharyngitis.[1,2] Throat culture is the diagnostic test of choice for group A streptococci[3] which is time consuming. This time delay may cause issues with appropriate follow-up treatment. The period of communicability is reduced if GAS is treated early in the clinical course. So several rapid antigen detection tests for GAS have been developed to detect streptococcal group A carbohydrate from throat

swab. The rapid detection tests are highly specific but not as sensitive as routine throat culture.[3]

Fusobacterium necrophorum is now being recognized as a common agent of endemic pharyngitis in young adults.[1] The clinical signs and symptoms of pharyngitis caused by F. necrophorum may be indistinguishable from those causing GAS pharyngitis. There is potential for the severe complication of Lemierre's syndrome. Patients with Lemierre's syndrome initially present with symptoms of pharyngitis, tonsillitis, or peritonsillar abscess and show initial clinical improvement .Approximately 4 days after clinical improvement of pharyngitis, the signs and symptoms of bacteremia associated with Lemierre's syndrome may appear. F. necrophorum should be a major consideration in the treatment of pharyngitis in adolescents and young adults due to the severity of complications caused by F. necrophorum, Vincent angina or trench mouth is a distinct but rare form of necrotizing ulcerative gingivitis. This is associated with severe pain, tissue destruction, grey pseudo membrane formation, putrid discharge, fever, malaise and cervical lymphadenopathy. The bacterial agent is not well established; however anaerobic spirochetes have been isolated at the advancing edge of inflamed tissue.

Pharyngitis associated with Epstein-Barr virus (EBV) is also known as infectious mononucleosis (IMN).[4] It is a common etiology of throat pain, especially in adolescents. The most common mode of transmission is oral contact. EBV produces the mononucleosis syndrome, which consists of fever, malaise, headache, pharyngitis, dysphagia and odynophagia.[4] Examination shows normal-sized or hypertrophic tonsils, palatal petechiae, and large, tender cervical lymphadenopathy. Tonsils may have a white or grey membrane that look identical clinically to diphtheria & streptococcal pharyngitis. Rash is rare and occurs most commonly in patients who have been treated with amoxicillin. Most patients have splenomegaly, and some have hepatomegaly. Diagnosis of EBV can be confirmed by laboratory investigations.[5] White blood cell counts typically range from 10,000 to 20,000/µl with a marked lymphocytosis and atypical lymphocytes in peripheral smear. Serum transaminase, alkaline phosphatase, and bilirubin levels may all be elevated, although few patients manifest jaundice. Previously the most commonly used diagnostic assay was the heterophile agglutination test, which measures immunoglobulin M antibodies, which are not specific to EBV antigens but are produced by EBV-stimulated B cells. However, only 40% to 60% of patients with infectious mononucleosis have a positive result within the first week after onset of the illness, and 80% to 90% have a positive result 1month after onset.[5] Presently EBV-specific serologic assays have become the method of choice for confirmation of acute or convalescent EBV infection. IgM VCA(viral capsid antigen) antibodies indicates acute EBV infection, Polymerase chain reaction assays on blood or plasma can be used for EBV DNA quantification and is a useful diagnostic test.[5] The sequelae include airway obstruction, splenic rupture, encephalitis or myocarditis.

Diphtheria is rare in developed countries because of widespread vaccination but is very common in developing countries like India.[6] After the introduction of Universal Immunization Program(UIP) in India, there has been a decreasing trend of diphtheria cases. Still nearly 2000-4000 cases are reported annually.[7] Kerala state has high immunization coverage of around 82% and better health indices compared to rest of India, however diphtheria outbreaks were reported during four consecutive years-2015,16,17 and 18 in Kerala despite these favorable factors.[8] According to the national level surveys, the coverage of three primary diphtheria vaccines ranged between 55.1% (1998–1999) and 78.4% (2015–2016).[8]

The majority of respiratory infections caused by toxin producing strains of Corynebacterium diphtheriae are tonsillopharyngeal. Sore throat is the most common symptom of diphtheria and is usually accompanied by fever and malaise. Formation of a membrane on the tonsil or pharyngeal surface is the hallmark of diphtheria but occurs in only one-third of patients. The membrane that forms in diphtheria is white early in the course of the illness, becomes dark grey and leather-like later and attempts to dislodge the membrane potentially causes bleeding. Membrane formation is due to local toxin production, and is composed of necrotic fibrin, leukocytes, erythrocytes, epithelial cells, and organisms. Spreading of the membrane heralds development of systemic toxicity. Extensive spreading of the membrane can occur to involve the larynx, nasal passages and tracheobronchial tree. Massive swelling of tonsils, uvula, nodes in cervical, submandibular and anterior neck region causes the bull neck appearance. Continued progression may lead to respiratory distress and death. Systemic complications of toxin include cardio toxicity and neurotoxicity. Definitive diagnosis of diphtheria requires culture of C. diphtheriae from respiratory tract secretions, and a positive toxin assay.

Oropharyngeal candidiasis also called thrush presents with white patches in the mouth, loss of taste, and sometimes dysphagia & odynophagia.[9] Many would be asymptomatic. It is common in those who wear dentures; patients treated with antibiotics, chemotherapy, malignancy, diabetes mellitus and those with cellular immune deficiency like AIDS. Patients who are treated with inhaled glucocorticoids for asthma are also at risk. Immunosuppressed patients with thrush often have concomitant Candida esophagitis. The diagnosis is evident from the presence of white plaques on the buccal mucosa, palate, tongue, or the oropharynx or under dentures, where there is usually erythema without plaques. The diagnosis can be confirmed by scraping the lesions with a tongue depressor and performing a Gram

stain or KOH mount on the scrapings. Budding Candida yeasts with or without pseudohyphae are seen.

Diphtheria is an ongoing epidemic in Kerala since 2016. However, we had a group of young immunized patients admitted with membranous tonsillitis clinically mimicking diphtheria but with unique investigational profile different from that of diphtheria. Based on this PCR and antibody testing of IMN was done and found positive.

MATERIALS AND METHODS

Data was collected from the records of patients admitted as diphtheria in infectious diseases ward during the epidemic period of 2018. When the clinical and hematological profile was found different from diphtheria, EBV PCR and Ig M VCA was sent to Microbiology department of our institution and State Virology Lab, Alleppy.

OBSERVATION

We had 18 patients with proved IMN. All had history of full dose childhood vaccination. All these patients were young, had regional adenopathy bilaterally, membrane in throat, tonsillar enlargement, elevated total count with lymphocyte predominance and peripheral smear showing large numbers of atypical lymphocytes. Elevated liver enzymes were seen in 14 patients with values > 5 times upper limit of normal in 6 patients. None had splenomegaly clinically and USG wise. CRP was only mildly elevated in all except one patient who had very high value (169). All had Ig M VCA positivity. EBV PCR was done in 11 patients and all were positive. All Diphtheria patients had very high ESR, CRP, polymorphonuclear leucocytosis and normal liver enzymes.

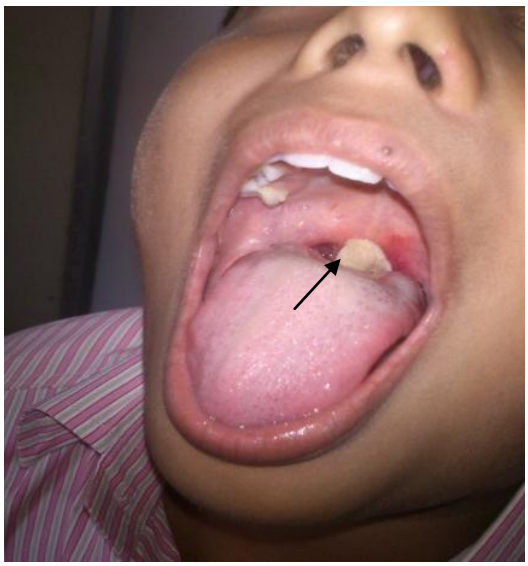

Figure 1: Membrane in throat.

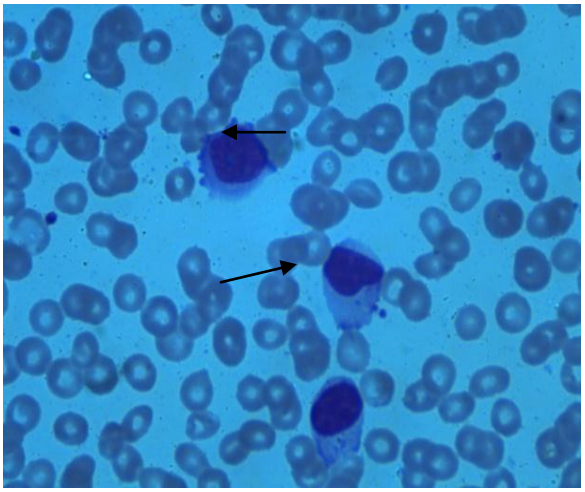

Figure 2: Atypical lymphocytes in peripheral smear.

Table 1: Clinical and Laboratory profile of 18 patients.

No	Age	Fever days	Odynophagia days	Membrane	Immunisation	TC	DC	ESR	CRP	EBV PCR	EBV VCA	PS atypical lymphocytes	LFT OT/PT/ALP
1	15	10 d	4 d	+	yes	15500	P23 L66	23	13	+	+	26%	62/37/70
2	21	7	4	+	yes	23600	P22 L75	35	12	+	+	30%	99/136/98
3	18	2	3d	+	yes	19800	P 28 L65	35	1.8	+	+	12%,	60/71/121
4	15	2	2	+	yes	10700	P48 L 50	46	4	+	+	18%,	21/26/239
5	15	10 d	4d	+	yes	16200	N 27 L64	28	6.5	+	+	20%,	216/187/109
6	14	3	2	+	yes	28800	N31 L 69	45	2	+	+	25%,	98/62/134
7	24	2	2	+	yes	15100	N39 L 46	20	25	+	+	26%	69/83/121
8	29	5	5	+	yes	8500	P40 L57	45	crp-19	+	+	15%	246/296/125
9	25	2	2	+	yes	11600	P44 L39	38	2.4	+	+	12%,	83/106/73
10	15	nil	11	+	yes	16200	P 38 L64	18	6.5	+	+	20%	216/187/109
11	14	4	3	+	unknown	19400	N29 L63	24	21	+	+	18%	172/278/263
12	22	6	4	+	yes	10900	l67	33	0.54	NA	+	24%	167/333/177 BT/BD-3/1.5
13	16	7	3	+	yes	19300	P20 L68	42	9.79	NA	+	50%	41/47/72
14	16	nil	5	+	yes	21700	P33 L 61	50	12	NA	+	50%,	158/269/175
15	52	3	3	+	no	6100	P45 L53	11	169	NA	+	12%	124/116/88
16	18	14	7	+	yes	15400	N26 L67	8	7.8	NA	+	15%	32/40/160
17	20	30	14	+	yes	14400	P28 L65	40	5.3	NA	+	25%	441/409/145
18	20	5	4	+	yes	19400	P20 L74	22	10.2	NA	+	30%	174/247/100

DISCUSSION

Diphtheria and IMN are common differential diagnosis for acute membranous tonsillitis. IMN and diphtheria have many features in common like membranous pharyngotonsillitis, cervical lymphadenopathy, fever and malaise. However some unique features help to differentiate between the two.[10,11]

This include

1. Rash is seen only in IMN
2. Splenomegaly & hepatomegaly in IMN
3. Transaminase elevation & lymphocytic leukocytosis with atypical lymphocytes in IMN
4. Minimally elevated inflammatory markers like ESR & CRP in IMN, which are raised markedly in diphtheria

The treatment of diphtheria includes antibiotics and diphtheria antitoxin.[12] Being highly infectious, patients should be placed in respiratory droplet isolation, which should be continued till two throat cultures taken 24 hours apart are negative. The administration of antitoxin is an emergency as it prevents further toxin binding to neuronal and cardiac cells. Hence when there is strong clinical suspicion in the form of unvaccinated child presenting with membraneous pharyngo tonsillitis, in the back ground of epidemic in the locality, antitoxin is advisable without a laboratory proof. The laboratory identification may be delayed up to 48 hours. Management of IMN is symptomatic only.

The main factors which helped us to consider IMN were history of childhood vaccination with elevated total count and lymphocyte predominance, altered liver function tests on day 1 of admission itself, normal to mildly elevated ESR and CRP and atypical lymphocytes in peripheral smear. None of these patients had hepatomegaly or splenomegaly either clinically or ultrasound wise. These investigations were available within few hours. This avoided the empiric use of diphtheria antitoxin, the average consumption per patient was 60-80,000 units amounting to a total cost of 7,500-10,000 rupees. Also we could avoid unnecessary antibiotic exposure and prolonged hospital stay which was needed for diphtheria.

Cases of membranous tonsillitis in completely immunized patients and negative bacterial culture should awaken the possibility of IMN if compatible clinical & laboratory features are present and should be tested for EBV serology or PCR for confirmation.

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Conflicts of interest – nil.

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