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Diagnostic Approach to a Case of Serositis

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Abstract

Effusions can be labeled as inflammatory (exudative) or non-inflammatory (transudative) depending upon the pathophysiological process involved. Various biomarkers (fluid glucose, fluid proteins, fluid albumin, protein ratio, protein gradient, albumin gradient) have been proposed for the same. In this study, we analysed all these biomarkers against the gold standard (cytology) and the practical utility of fluid adenosine deaminase (ADA) for diagnosing Tubercular serositis in a Tuberculosis prevalent area like that of ours. We found that albumin gradient proves its versatility in differentiating the pathophysiological nature of the effusion. We henceforth propose a minimum must step ladder diagnostic algorithm for a case of serositis, thereby cutting the costs of evaluation.

Keywords: Effusion; Exudative; Transudative; Inflammatory; Non-inflammatory; Biomarkers; Serositis; ADA; Albumin gradient; Diagnostic algorithm

Introduction

Collection of fluid in serous cavity is termed as effusion and depending upon the topographical distribution, these can be further classified as being pleural/pericardial/peritoneal. Further classification is based on the underlying pathophysiological process involved, i.e., inflammatory/non inflammatory. Classically, the lights criteria had been proposed for this purpose, but it has certain drawbacks. Various other modifications have been proposed but each biochemical marker falls short in some or the other aspect. In our study, we did a critical review and analysis of each of the commonly used biomarkers, so as to ascertain which one of them is the most accurate. Fluid ADA has long been used for diagnosing Tubercular serositis, though presumptively. However, it has been found to be significantly raised in other lymphocytic effusions such as collagenosis, malignancies, etc. It is clear clear that raised ADA levels don't pathognomically indicate tuberculosis but how far does this holds true in a tubercular endemic zone like that of ours is the need of the hour. We analyzed the accuracy of fluid ADA for tubercular serositis and based upon our findings, we propose a step ladder diagnostic approach to a case of serositis.

Methods

Study setting, design and population

The study was conducted at a rural teaching hospital in central India. It was a prospective study and we enrolled all consecutive patients aged 12 years and above who were admitted in the medicine ward and found to have serous cavity effusion. The study population consisted of 247 patients admitted in Medicine department from 1st Dec 2012 till 1st Sept 2014 having pleural effusion and/or ascites. The diagnosis of effusion was supported by X-ray or ultrasonography and by direct tapping. All patients having pleural effusion or ascites were included in the study. Patients who did not consent for diagnostic tapping, patients having non-trappable effusion even under radiological guidance, patients in whom all required investigations to reach the final diagnosis could not be done (financial constraints), patients in whom exact etiological diagnosis was not found, and patients who were lost to follow up or died before exact etiological diagnosis could be determined were excluded from the study. The study flowchart has been depicted in the Figure 1.

Study procedure

Step 1: After determining the eligible patients for our study, detailed history was obtained and patient underwent general and physical examination and a tentative diagnosis of inflammatory/non-inflammatory effusion was made depending upon the criteria (Table 1).

Step 2: The next step was gross examination of fluid and commenting on whether it is inflammatory/non-inflammatory. Turbid, straw, haemorrhagic and frank pus were regarded as being inflammatory and serous/transparent as non-inflammatory.

Step 3: This was followed by complete biochemical analysis and the effusion was labelled as being inflammatory/non-inflammatory by applying cut offs for each marker (Tables 2 and 3).

Step 4: Cytological analysis: Each fluid was analysed cytologically and was then labelled as being inflammatory/non-inflammatory (Tables 2 and 3).

Step 5: Fluid ADA was sent for all fluids and other tests for etiological diagnosis such as fluid amylase, cell block analysis were performed. Etiological diagnosis was made in cases of tuberculosis depending upon the response to therapy.

Step 6: The sensitivity, specificity of each of these parameters (for differentiating inflammatory from non-inflammatory) were assessed with cytology as the gold standard. Statistical analysis was carried out with the Stata ver 13, Epi info software.

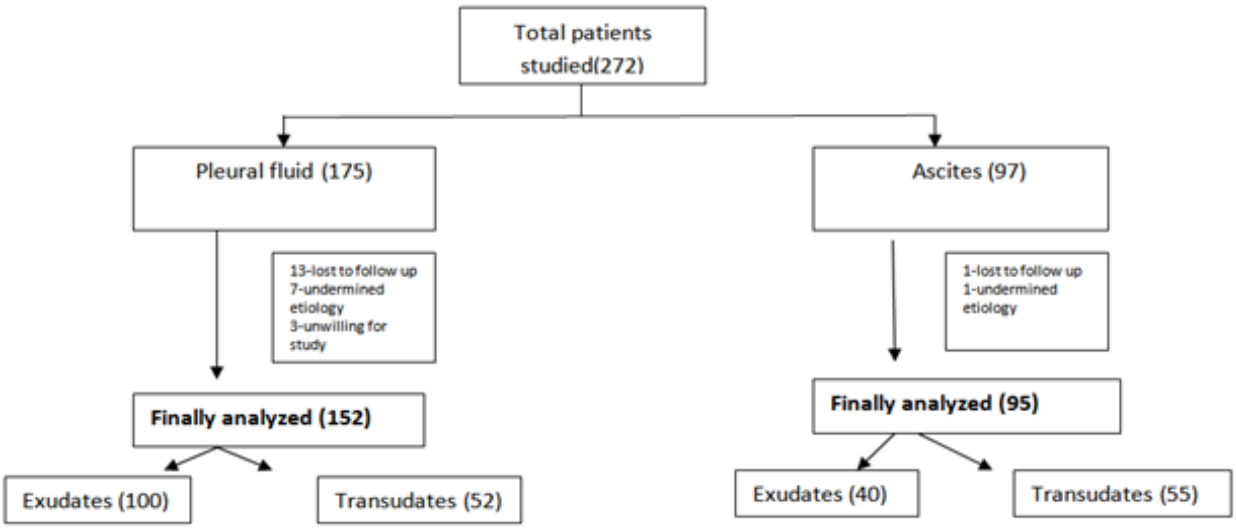

Figure 1: Study flowchart.

Location	Inflammatory (Exudative) Initial Denominator: Absence of Edema Disorder	Non inflammatory (Transudate) Initial denominator: Presence of Heart Failure or Oedema Disorder
Pleural	Significant weight loss, Pleural effusion without mediastinal shift, Pleural effusion with dyspnoea, Left sided pleural effusion, Accompanying localised crackles and Bronchial breathing, Pleural pain, rub and Intercostal tenderness	Bilateral pleural effusion with predominant right sided involvement, Signs of hepatocellular failure/renal failure (anaemia, hypertension)
Ascites	Isolated ascites, pain ,tenderness, guarding and rigidity, coexisting fever	Pedal edema coexisting with dominant ascites
Features of malignant etiology (common to all)	Significant weight loss in old, lymphadenopathy with evidence of ediastinal compression, massive pleural effusion without mediastinal shift, Hard liver, Breast nodule, Thyroid nodule, paraneoplastic masnifestations as Gynecomastia, clubbing) mass in abdomen arising from pancreas liver/ovary/intestinal), left supraclavicular lymphadenopathy , evidence of necrotizing disease in the form of Hemoptysis, hematemesis	
Features of tubercular etiology (common to all)	Matted glands, apical or apical segment of lower lobe affection, low grade fever, weight loss in young	

Table 1: Clinical features for labeling an effusion as inflammatory/non-inflammatory.

Parameter	Cut off for inflammatory	Cut off for Non inflammatory	References
Fluid protein	>3 g/dl	<3 g/dl	[1-4]
Fluid protein/serum protein ratio	>0.5	<0.5	[4-6]
Fluid protein-serum protein gradient	<3.1 g/dl	>3.1 g/dl	[4,7]
Fluid albumin-serum albumin grad	<1.2 g/dl	>1.2 g/dl	[4,6]
Absolute Fluid LDH	>200 U/L	<200 U/L	[6,8-10]
Fluid LDH/Serum LDH ratio	>0.6	<0.6	[4]
Fluid glucose	<60 mg/dl	>60 mg/dl	[11,12]
Fluid cholesterol	>45 mg/dl	<45 mg/dl	[4,8,12]
Cytology	Total leucocyte count >425 cells/ cumm	Total leucocyte count <425 cells/ cumm	[13]

Table 2: Criteria for pleural/pericardial effusions.

Parameter	Cut off for inflammatory	Cut off for non inflammatory	References
Fluid protein	>2.5 g/dl	<2.5 g/dl	[14,15]
Fluid protein/serum protein ratio	>0.5	<0.5	As applied for pleural fluid
Fluid protein-serum protein grad	<3.1 g/dl	>3.1 g/dl	As applied for pleural fluid
Fluid albumin-serum albumin grad	<1.2 g/dl	>1.2 g/dl	[16]
Absolute Fluid LDH	>200 U/L	<200 U/L	[9,17]
Fluid LDH/Serum LDH ratio	>0.4	<0.4	[17]
Fluid glucose	<50 mg/dl	>50 mg/dl	[17]
Cytology	Total leucocyte count >250 cells/ cumm	Total leucocyte count <250 cells/ cumm	[18-20]

Table 3: Criteria for ascites.

Results for pleural fluids

The protein gradient, albumin gradient were highly sensitive and specific irrespective of etiology. Though glucose ratio and fluid glucose were 100% specific but their sensitivity was low owing to their indecisive behaviour in non lymphomatous malignant pleural effusions (Table 4).

Parameter		Sensitivity	Specificity	P value
Clinical assessment		98%	94%	0.001
Gross examination		99%	92%	0.01
Bio chemicals	Fluid total protein	92%	93%	0.01
	Fluid Protein ratio	92%	93%	0.001
	Fluid Protein gradient	92%	97%	0.01
	Fluid albumin gradient	92%	100%	0.01
	Fluid LDH,LDH ratio	89%	92%	0.01
	Fluid glucose	85%	87%	0.01
	Fluid ADA (41IU/L)	94%	97%	0.01
	Fluid ADA (37 IU/L)	100%	97%	0.01

Table 4: Results for pleural fluids.

Results for ascitic fluids

Though the sensitivity of fluid total protein, protein ratio and protein gradient are same as albumin gradient, the specificity was less as compared to albumin gradient (Table 5).

Parameter		Sensitivity	Specificity	P value
Clinical assessment		90%	98%	0.001
Gross examination		97 %	94%	0.01
Biochemicals	Fluid total protein	70%	94%	0.01
	Fluid Protein ratio	70%	98%	0.001
	Fluid Protein gradient	70%	94%	0.01
	Fluid albumin gradient	70%	100%	0.01
	Fluid LDH, LDH ratio	72%	94%	0.01
	Fluid glucose	65%	100%	0.01
	Fluid ADA (25 IU/L)	100%	94%	0.01
	Fluid ADA (37 IU/L)	100%	98%	0.01

Table 5: Results for ascitic fluids.

Discussion

Protein parameters in confirmation of exudative/ transudative nature of fluids

In our study, irrespective of etiology, protein gradient (<3.1g/dl for exudates and >3.1 for transudates) and albumin gradient (<1.2 for exudates and >1.2 for transudates) remain as the universal criteria to differentiate exudates from transudates. Fluid protein and protein ratio may fall in exudative range in patients of oedema disorders with transudative fluids when on prolonged diuretic therapy (so called transexudates) but the albumin gradient depicts its true transudative nature. In our study, albumin gradient exhibited sensitivity of 92% and specificity of 100%. Romeiro et al. also proposed protein gradient and albumin gradient to be superior to total proteins and protein ratio in differentiating true exudates from false exudates. The possible mechanism explains the selective intrapleural/peritoneal dehydration owing to shift of fluid into the intravascular compartment which is volume depleted following the use of diuretics [15,21] (Table 6).

Albumin gradient in differentiating pleural effusions

Albumin gradient exudate /transudate	Cytologically inflammatory (100)	Cytologically non inflammatory (52)
Inflammatory/Exudate (Albumin gradient<1.2)	92	0
Non inflammatory/ Transudate (Albumin gradient >1.2)	8-Malignant pleural effusions	52
Sensitivity-92% (84.8 to 96.47) Specificity-100% (93.08-100) PPV-100%, NPV-86% Neg LR-0.08 (0.04 to 0.16) P<0.001		

Table 6: Albumin gradient in differentiating pleural effusions.

Relative accuracy of protein and albumin gradient in doubtful cases

Etiologies	No.	Total Prot. (with range)	Prot. Ratio (with range)	Prot.Gradient (with range)	Albumin Gradient* (with range)
		Ex>3	Ex<0.5	Ex<3.1	Ex<1.2
		Tr<3	Tr>0.5	Tr>3.1	Tr>1.2
CCF	3	3 (Exu) 3.1-3.3	0.65 (Exu) 0.61-0.67	3.4 (trans) 3.2-3.5	1.4 (trans) 1.3-1.5
Hepatic hydrothorax	1	3.1 (Exu)	0.57 (exu)	3.2 (trans)	1.3 (trans)

Table 7: Relative accuracy of protein and albumin gradient in doubtful cases.

Thus from Table 7, we see that the misclassified cases of CCF and hepatic hydrothorax which were protein concentrated because of long term diuretic therapy, were well screened transudative by the protein gradient and albumin gradient.

SAAG in determining the pathological nature of ascitic fluids

SAAG exudate/transudate	Cytologically inflammatory (40)	Cytologically non inflammatory (55)
Inflammatory/Exudate (n=28) (SAAG<1.1)	28	0
Non inflammatory/ Transudate (n=67) (SAAG>1.1)	12 (10-SBP 2-Malignant ascites)	55
Sensitivity=93.33% (77.93% to 99.18%)		
Specificity=100.00% (93.51% to 100.00%)		
Negative Likelihood Ratio=0.07 (0.02 to 0.25)		
Positive Predictive Value=100.00% (87.66% to 100.00%)		
Negative Predictive Value=96.49% (87.89% to 99.57%)		
P <0.01		

Table 8: SAAG in determining the pathological nature of ascitic fluids.

Thus from Tables 8 and 9 we can conclude that SAAG has an edge in distinguishing transexudates from true exudates but has limited efficacy in diagnosing SBP, malignant ascites.

Superiority of SAAG over protein analysis misclassified cases

From Table 9, we can say that albumin gradient identifies false positive exudates as the best.

Glucose ratio and fluid glucose: Glucose ratio (<0.5 for exudates and >0.5 for transudates)or fluid glucose (<60mg/dl for exudates and >60 mg/dl for transudates) though were 100% specific in delineating exudative/transudative nature of fluids, their indecisive behaviour in malignant (non lymphomatous) serositis, SBP, Scrub typhus and pancreatic effusions brings down sensitivity and doesn't stand the test of universal criteria. Low levels of glucose (<30 mg/dl) depicted in cases of non-tubercular empyemas and SLE associated polyserositis can be explained by the decreased transport of glucose into the fluid (SLE) and increased utilization in cases of empyemas [22].

	No.	Total protein levels	Protein gradient	Albumin gradient
		Exu>2.5, Trans<2.5	Exu<3.1, Trans>3.1	Exu<1.1, Trans>1.1
CCF	1	2.9 (Exu)	2.8 (Exu)	1.3 (Trans)
Nephrotic syndrome	1	2.7 (Exu)	3.2 (Trans)	1.4 (Trans)
Acute kidney injury	1	2.8 (Exu)	3.3 (Trans)	1.2 (Trans)

Table 9: Superiority of SAAG over protein analysis misclassified cases.

LDH ratio and fluid LDH: LDH ratio and fluid LDH are selective and inconsistent. LDH ratio and fluid LDH do not necessarily reflect exudative/inflammatory nature with all non lymphomatous mailgnant serositis. In 1 out of 22 cases of Non lymphomatous malignant effusion and 1 out of 2 cases of non-tubercular empyemas, the levels crossed the serum levels. The possible explaination is the high cells turn over associated with malignancies and the high grade inflammations seen in empyemas [4].

Significance LDH isoform estimation: Remy and his associates demonstrated that the enzyme profile of transudates only differs from that of normal serum by a slight increase in isoLDH 4 and 5 [23]. In exudates this profile is the reverse of the normal serum profile, with a decrease in isoLDH 1 and 2 and an increase in isoLDH 4 and 5. A more than 30% rise in isoLDH 2 is in favour of a malignancy (mesothelioma excluded). Polymorphonuclears contain more isoLDH 4 and 5 than mononuclears; the high content seems to be due, at least partly, to release of these enzymes by the polymorphonuclears and/or mononucleate cells involved in pleural inflammation [23]. In our study, we couldn't estimate the isoform patterns in effusion because of the lack of resources. We therefore question the rationale behind ordering LDH analysis in routine for all fluids given its limited differential value in judging the etiology of effusion.

Fluid cholesterol: High fluid cholesterol (>45 mg/dl) was observed with lymphomatous malignancy, tubercular/pyogenic empyema, parapneumonic effusions. It was not raised in SLE, Scrub Typhus and acute Tubercular effusions. The cases of tubercular pleural effusions and non lymphomatous malignancies of long standing nature (>4 months) accumulated high fluid cholesterol content in our observation.

These effusions which have raised cholesterol content have been traditionally termed as cholesterol effusions/pseudochylothorax/

chyliform effusions obvious on gross examination. The pathogenesis of cholesterol effusions is uncertain. A traditional theory proposes that lysis of erythrocytes and neutrophils in pleural fluid releases cholesterol and other lipid constituents from degenerating cell membranes; these compounds are "trapped" in the pleural space by the thickened pleural membranes. Eventually, these lipid constituents become concentrated and impart the milky quality to the pleural fluid [24]. The occurrence of cholesterol pleural effusions in patients without pleural fibrosis, however, suggests that a more active but yet-to-be defined intrapleural process may exist that concentrates cholesterol in pleural fluid. One theory to explain this observation is that the pleural cholesterol is derived from serum lipids bound to low density lipoproteins (LDL) that accumulate in the pleural space during acute inflammation [25]. Over time, lipoprotein binding of cholesterol shifts from LDLs to high density lipoproteins (HDL). The mechanism for this shift in lipoprotein binding is poorly understood.

The relation between chronicity of effusions and high cholesterol content can be explained by the cellular lysis which leads to the release of lipid components from the phospholipid bimembrane of cells [26].

Inconsistency of fluid cholesterol levels in inflammatory fluids makes it selective criteria. The routine estimation in all inflammatory fluids is not advocated.

Rationale for reliability on ADA as an affirmation to start antitubercular therapy: Practical utility of ADA, can it be used blindly to diagnose tubercular serositis?

Being clinicians we are more worried about the applicability of a tool bedside; and so at the end of the day we are left with 3 immensibely important practical issues:

- Can ADA alone subsitute other conventional tests for diagnosing tubercular affections?
- Do we need to wait for response to therapy as a tool for retrospective diagnosis of tuberculosis or straightway we rely on ADA levels to start antibutbercular therapy?
- How far successful shall it be to implement ADA as a primary investigatory weapon during the early steps of fluid analysis?

To solve these questions, lets take a broader look! Demonstration of AFB, by microscopy and AFB culture are the various means to confirm the etiology of tuberculosis. Visualization of AFB in directs smears or in cultures is usually difficult [27] and in most cases negative. Histopathological evidence of tubercular pleuritis (invasive method) also is rare to demonstrate. Newer methods such as those involving the amplification of bacterial DNA by the PCR and comparable systems demonstrate only the antigen but don't detect the active disease in endemic society. They are not available for widespread use in the developing countries like India and especially in a rural set up like ours.

ADA activity, a marker of T-cell activation and cell-mediated immune response can help differentiate tubercular etiology from non-tubercular. Piras et al. [28] were first to report high ADA in tubercular pleural effusion. Gotu et al. [29] did a meta-analysis of studies (conducted between 1966 and 1999) to conclude that the test performance was reasonably good. Ocana et al. and Valdes et al. [30,31] even reported high sensitivity and specificity, postive predictive value and negative predictive value in larger sample size studies.

Results of our study indicated that ADA levels in the aspirated fluid are of considerable value in differentiating between tubercular and non-tubercular disease with fairly high accuracy and sensitivity at the proposed cutoff.

In inflammatory serositis, literature defines a cut off level of 41 IU/L. We found it to be 37 to reach to 100% sensitivity. The specificity of ADA in confirming tubercular serositis we found was 98% because ADA positivity was also shared by other necrotizing lymphocytic effusions (1 out of 22 Non Lymphomatous and 2 out of 2 lymphomatous malignancy) and 1 pyogenic empyema.

It is possible to reach to the conclusion of inflammatory and non-inflammatory nature of serous fluid with biochemical parameters and cellular response on cytology in all study subjects. We pooled together all inflammatory serositis (pleural,peritoneal and pericardial),the sensitivity and specificity of fluid ADA (37 IU/L cut off),for diagnosis of tubercular pathologies we found was 100% and 95% respectively. This gap in specificity can only be filled up by therapeutic follow up.

We had to rely on confirmation of tuberculosis by therapeutic trial in 43 out of 66 cases of tubercular serositis. All were ADA positive at the beginning of therapeutic trial. No case turned out to be lymphomatous malignancy on follow up.

Summarising

The most frequent disease presenting with serositis in our setting is tuberculosis. The pathophysiology that pours fluid in serous cavities in tuberculosis is the hypersensitivity phenomenon to the tubercular antigen.

It is no wonder that demonstration of AFB bacilli is so rare with tubercular effusions. Biopsy of the serous membrane for histopathological confirmation of tuberculosis is not performed in day to day practice.

The clinical suspicion of tuberculosis (weight loss, mild grade prolonged fever, loss of appetite) is most frequent in our setting, a lymphocytic effusion is empirically put on therapeutic trial and the patient is followed up for recovery, i.e., clinically (weight gain, fever settling down, improved appetite) and by radiological resolution, thus confirming tubercular etiology. One has to wait for say a month or two for response of therapy.

The need to increase the probability of tubercular etiology at the time of provisional diagnosis is filled up by fluid ADA levels.

Recommendation

For bedside approach approach to a patient of serositis, we propose an algorithm which caters all steps in the assessment of a suspected case of serositis. Right from clinical examination to the tests for etiological confirmation, the algorithm takes into account the accuracy and applicability of each parameter which must be obligate for the correct diagnosis of serositis. The important pillars helping in making a diagnosis are outlined as follows (Figure 2).

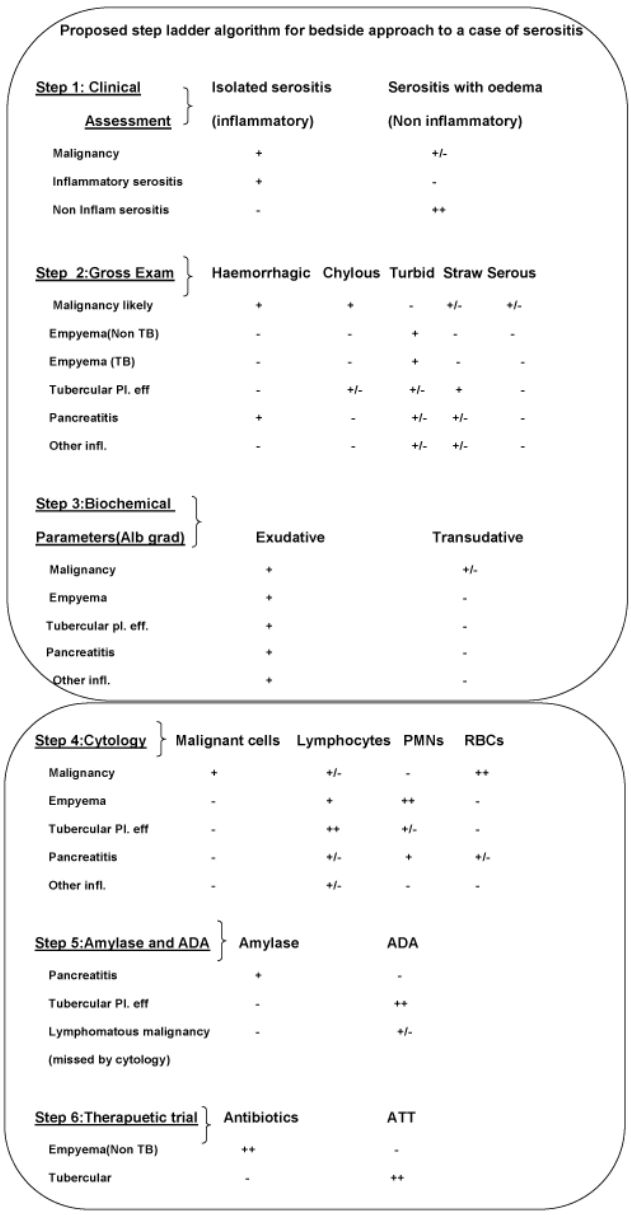

Figure 2: Proposed step ladder algorithm for beside approach to a case of serositis.

Step 1: Bedside clinical assessment remains an important pivot around which whole of the work up of a patient of serositis rotates.

Step 2: Gross examination of the fluid when combined together with the clinical acumen may itself suggest a diagnosis with high accuracy.

Step 3: Biochemical assessment: Amongst the biochemical parameters, albumin gradient stands the test of being a universal discriminiator for determining the nature of effusion whether it is inflammatory/non inflammatory irrespective of etiology.

Step 4: Cytology is the cornerstone in the confirmation of the pathological nature of fluids. Along with this, it plays an important role as an etiological confirmator in cases of malignancy which bluffs when biochemical criteria are applied.

Step 5: ADA

Most frequent disease presenting with serositis in our setting is tuberculosis. The hypersensitivity phenomenon responsible for this serositis rarefies the demostration of AFB bacilli with tubercular effusions. Invasive procedure like pleural biopsy for histopathological evidence has low output and is futile in day to day practice.

Since lymphocytic turbid, haemorrhagic, chylous effusions are already filtered out in the initial gross examination and malignancy gets detected by cytological confirmation, what remains at stake is the etiology of straw coloured exudative fluids.

High fluid ADA level offers enhanced probability of tubercular etiology at the time of provisional diagnosis.

With the clinical suspicion of tuberculosis (weight loss, mild grade prolonged fever, loss of appetite), the empirical therapeutic trial of antitubercular therapy for a predominantly straw coloured lymphocytic effusion with high ADA content and observing for recovery by clinical (weight gain, fever settling down, improved appetite) and radiological means did not deceive us.

We hence consider a straw coloured lymphocytic effusion with high ADA content confirmatory for the diagnosis of tubercular serositis.

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