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INCREASINGLY COMMON PRESENTATION OF EXTRANODAL BURKITTS LYMPHOMA WITH SURPRISINGLY RAISED PLEURAL/ASCITIC FLUID ADENOSINE DEAMINASE LEVELS

Clinical Research

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ABSTRACT

Acute onset polyserositis as a presentation of Non Hodgkins lymphoma(NHL) occurs in 20% of individuals.(1-4) Etiology being a jumble between an Extranodal Burkitt lymphoma(ENBL),a pyothorax associated lymphoma and a primary effusion lymphoma as a cause of such effusions.(5) We report a case series of 5 such patients of NHL,four of which received chemotherapy with standard CHOP regimen.However,all patients succumbed.The common findings of strikingly raised fluid adenosine deaminase(ADA) levels in all of these effusions establishes a possible etiopathological link(ENBL).(6) An immunocompetent status renders primary effusion lymphoma unlikely which also has high fluid ADA levels.This case series proposes a rational approach towards such cases of suspected ENBL presenting with acute onset lymphocytic polyserositis and a negative HIV antibody status with enormously raised fluid ADA levels thereby permitting timely institution of chemotherapy for a better patient prognosis.

KEYWORDS

Polyserositis,Non Hodgkins lymphoma,Primary effusion lymphoma,adenosine deaminase.

INTRODUCTION :

Haematological malignancies occasionally present with effusions. Most commonly,NHLs have been implicated in such effusions followed by Hodgkins lymphoma(HL) and least commonly by other malignancies such as acute myeloid and lymphoid leukemias, multicentric castleman disease and most rarely by multiple myelomas(5). Pathophysiologically,some malignant effusions are termed 'paramalignant' in case of effusion arising not from the direct invasion of pleura by the malignant cells e.g HL in which the effusion is because of the infiltration and secondary obstruction of the thoracic duct.

The case is altogether different in NHLs where the effusion is because of the direct pleural infiltration of the neoplastic clone of B cells.Primary effusion lymphoma (PEL) reveals a separate clinicopathological subtype of lymphoma associated effusions predominantly of B lymphocyte cellular dominance.The causative agent seems to be Kaposi sarcoma associated Human Herpes virus 8(HHV 8) seen mostly in patients of acquired immunodeficiency syndrome. Lymphadenopathy is conspicuous by its absence.Fluid ADA activity has been reported high in such cases reflecting a high lymphocyte turn over.(7) In one of the study conducted it was found that high pleural fluid ADA levels were directly proportional to the all cause mortality in patients with malignant pleural effusions(solid tumours as well as lymphomatous).(8)

Case 1 : 16 years female presented to the emergency department with history of acute onset rapidly progressive breathlessness.This wasn't accompanied with cough/fever/chest pain.She was restless,had tachycardia(140 beats/min),hypotension(80/50mmhg) and was tachypnoeic(RR 40/min).

Hypoxia was present(SpO2 82% on ambient room air) and she had elevated jugular venous pressure and mild pitting pedal edema.Her systemic examination revealed findings suggestive of a massive left sided pleural effusion causing a rightward mediastinal shift.Cardiac examination showed muffled heart sounds.

She had mild tender soft hepatomegaly without any ascites.A possibility of massive pleural effusion with pericardial effusion causing a cardiac tamponade was kept.Her electrocardiogram(ECG) revealed electrical alternans and chest radiograph (CXR) showed a massive left sided pleural effusion with a gross mediastinal shift towards the right(Image 1).A 2D echocardiogram(ECHO) revealed significant pericardial effusion causing right atrial,ventricular and left ventricular collapse(Image 2) and an increased interventricular dependence.

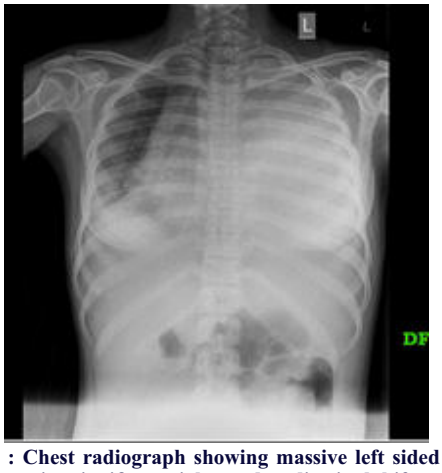

Image 1 : Chest radiograph showing massive left sided pleural effusion causing significant rightward mediastinal shift

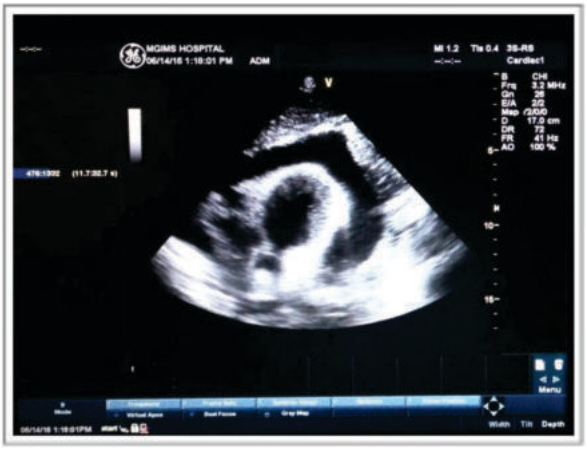

Image 2 : 2D ECHO showing massive pericardial effusion causing chamber collapse

Diagnostic cum therapeutic pleural paracentesis(1L) revealed a hemorrhagic exudative effusion with enormous lymphocytes and a significantly raised pleural fluid ADA levels(~700IU/L).A pleural fluid cell block was advised only to be reported inconclusive. Simultaneously,

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a pericardiocentesis(400ml) was performed to reveal almost similar findings.The patient improved significantly post procedurally(Image 3).

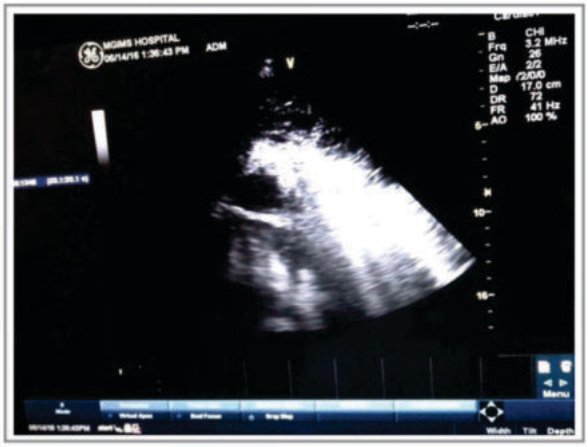

Image 3 : Check 2D ECHO post procedure showing reduction in the pericardial effusion

After having ruled out other causes of acute onset polyserositis (viz systemic lupus erythematosus,dengue,scrub typhus and an acute kidney injury),a therapeutic dilemma arose regarding the underlying aetiology and hence she was managed conservatively.The patient remained stable for the next 36 hours until when she again precipitated shock. Check 2D ECHO and a CXR again showed a massive pleural effusion and pericardial effusion causing hemodyanamic compromise. An intercostal tube (ICD) was inserted and about 2L of haemorrhagic pleural fluid was tapped.Pig tail catheter was inserted in the pericardial cavity and about 1500 ml of hemorrhagic fluid was removed.The patient again showed signs of recovery.However after 48 hours, she again deteriorated(imaging showed reappearance of significant pericardial and pleural effusions) and was started on vasopressors and invasive ventilation to which she didn't respond and succumbed to the illness.A post mortem pleural and pericardial biopsy was done only to reveal a NHL(Image s 4,5,6) the sub typing of which couldn't be done.

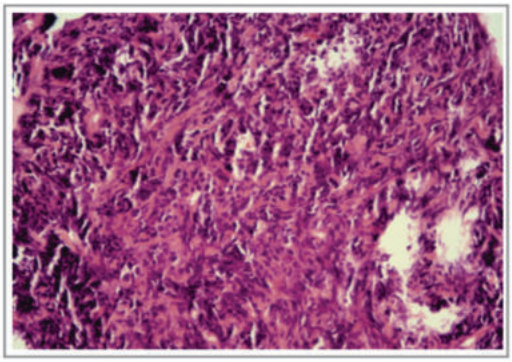

Image 4 : Pleural fluid cell block showing neoplastic lymphocytes (H & E stains,100X with oil immersion)

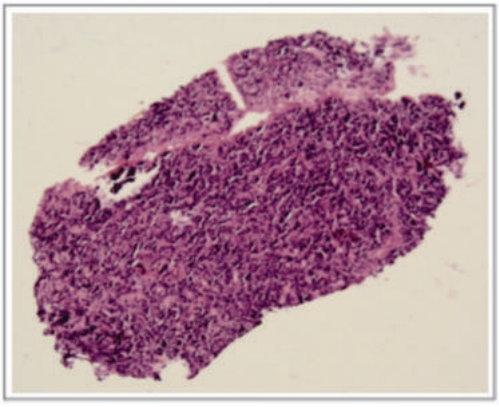

Image 5 : Pleural biopsy histopathology specimen of the same patient showing multiple neoplastic lymphocytes invading the underling interstitium(H & E stains,100X with oil immersion)

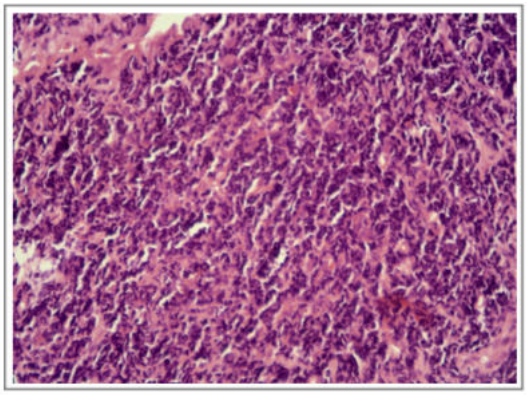

Image 6 : Pericardial fluid cell block of the same patient showing a dense population of neoplastic lymphocytes(H & E stains,100X with oil immersion)

Case 2 : A 34 years female presented to the emergency department with history of insidious onset gradually progressive breathlessness and low grade fever since last month.Appetite and weight loss accompanied the scene.She didn't have any chest pain/cough/swelling over feet/facial puffiness or any signs of a connective tissue disorder.She was febrile,tachycardic(HR 150/min),hypotensive(BP 70 systolic) and tachypnoeic(RR 38/min).An ECG,CXR and 2D ECHO showed electrical alternans,a moderate pleural effusion and pericardial effusion causing cardiac tamponade.A diagnostic pleural paracentesis showed a straw coloured lymphocytic exudative effusion with raised ADA levels of 143 IU/L

Pericardial fluid analysis showed similar results.Considering it to be Tubercular pleuritis,anti tubercular treatment was started.She responded and her haemodynamics improved and was then discharged.She however returned in a fortnight with progressive dyspnoea ,tachycardia and hypotension and was found to have massive pleural and pericardial effusion along with ascites.Therapeutic paracentesis followed by a histopathological analysis of the pleural fluid cell block showed it to be NHL.However before administering the first cycle of the standard CHOP regimen (cyclophosphamide, doxorubicin,vincristine and prednisolone) she deteriorated and finally succumbed.

Case 3 : A 38 years male patient had presented to us with the history of distended abdomen and swelling over the feet since last 3 months.He didn't have any malaena/hematochezia.He didn't complain of breathlessness,chest pain any oliguria/facial puffiness.He didn't run an evening rise.There was no alcohol dependence and no jaundice in the past. Never had he had a percutaneous needle exposure/unsafe sex.Upon admission,he had stable vitals,was anicteric with a normal JVP and pitting pedal edema.He had grade III ascites without any features of portal hypertension.Upon radio imaging,he had hepatomegaly without portal vein dilatation/splenomegaly.There were no mesenteric lymph nodes.Ascitic fluid was exudative(Serum ascitic albumin gradient 0.8) and was rich in lymphocytes.Ascitic fluid ADA was 91IU/L.Contrast enhanced computed tomography scan of the abdomen was performed to ascertain the cause of exudative ascites which revealed mucosal thickening in gastric pylorus. Histopathological analysis revealed it to be high grade NHL.Further sub typing couldn't be done because of resource constraints.The patient was adminstered 5 cycles of CHOP to which the response was dramatic with complete subsidence of ascites.However,the patient lost to follow up and returned in 6 months with tense ascites,gross pedal edema,massive left sided pleural effusion and dyspnoea.Diagnostic paracentesis of the pleural fluid and a cell block analysis revealed malignant lympohocytes.The pleural fluid ADA levels were 112IU/L.CHOP was again administered to which however the patient didn't respond well and finally died.

Case 4 : 17 years male presented with history of fever and night sweats.The examination was unremarkable only to reveal a single firm cervical lymph node on the right side.His CXR showed mediastinal widening and his ultra sonogram showed mesenteric lymph node enlargement.Fine needle aspiration cytology revealed NHL and was administered first cycle of standard CHOP regimen.His cervical lymph node melted with simultaneous disappearance of mediastinal and mesenteric lymph nodes.The patient followed up for the next 8 cycles

and later defaulted.After about 8 months,the patient presented with exudative ascites and exudative left sided pleural effusion with lymphocytic predominance.His cervical lymph node had increased in size with appearance of new lymph nodes.Pleural fluid cell block study revealed the presence of neoplastic lymphocytes.The pleural as well as ascitic fluid ADA were found to be significantly raised(96IU/L and 135IU/L) respectively. Inspite of another cycle of CHOP regimen being administered,the patient couldn't be saved.

Case 5 : 45 years male patient presented with history of fever and weight loss.He didn't have any respiratory complaints/ jaundice/ swelling over feet.His systemic examination was unremarkable. However a CXR showed mediastinal enlargement with left sided pleural effusion which was found to be exudative in nature and lymphocytic.Pleural fluid ADA was 209IU/L.Suspecting NHL,pleural fluid cell block study was advised which confirmed the diagnosis.The patient was then administered 9 cycles of the standard CHOP regimen to which he responded very well with complete regression of all lymph nodes.However inspite of a good patient compliance and regularly timed cycles,he again developed lymphomatous pleural effusion with similar biochemical and cytological characteristics.He deteriorated during the course of the hospital stay and finally succumbed to his illness.

DISCUSSION:

Non Hodgkin's lymphomas predominantly of the B lymphocyte type represent that major chunk of haematological malignancies which are infamous for their poor prognosis.En masse,they are characterised by 5 year survival rates ranging from 80% to 50% for low grade(follicular and marginal zone lymphomas) to high grade(Burkitts,Anaplastic and Pre B cell lymphomas).(9) Varying presentations,ranging from a completely asymptomatic incidental diagnosis to a highly catabolic state is the rule.Polyserositis, often acute has been described in about 20% of NHLs.(3) More commonly this blurry clinical entity has been frequently found to be picturesque in terms of the conspicuous absence of the traditional hallmark of NHLs i.e 'lymphadenopathy'.The subtypes of NHLs temporally associated with such domain are an extra nodal Burkitts lymphoma,a primary effusion lymphoma and the pyothorax associated lymphoma.Extranodal Burkitts lymphoma represents the notorious face of Burkitts lymphoma which is known for a delayed rather often a misdiagnosed presentation and a torrential course.It requires a modified CHOP ,the CODOX-M and IVAC (Cyclophosphamide,Vincristine,Doxorubicin,high dose methotrexate followed by Ifosfamide,Vincristine,Cytarabine,etoposide and intrathecal methotrexate), also called the Magrath regimen.(10-12) The prognosis still remains poor even with favourable International Prognostic Index scores(IPI).The polyserositis is exudative and lymphocytic with extremely raised fluid ADA levels(often > 100IU/L).

A direct head to head comparison in a Spanish study revealed significantly higher fluid ADA levels in NHL associated effusions as compared to tuberculosis.(13) It would not be a hyperbole to utter that pleural fluid ADA levels crossing the century mark make underlying tuberculosis unlikely. An unexplained lymphomatous effusion,with significantly raised fluid ADA levels can henceforth help a clinician in prognostication and initiation of early aggressive regimens for NHLs when awaiting the results of histopathological and immunohistochemical analysis.

Primary effusion lymphoma seen very commonly in patients of AIDS has been temporally linked to HHV 8 also known as Kaposi sarcoma associated HHV8.Simialr presentation as was with extra nodal Burkitts occur more commonly in PEL.A case report published highlighting the surprising association between PEL with peritoneal localisation and raised ADA levels,showed that fluid ADA levels might even be higher in PEL than in other subtypes of NHL.(14) The treatment regimens being similar to those for extra nodal Burkitts with a slight emphasis on the EPOCH regimen (etoposide, prednisolone, vincristine,cyclophosphamide and doxorubicin).(14-16) The difference is on the survival with PEL carrying a much grave prognosis.(6) Though PEL is a common in AIDS,case reports in otherwise negative HIV status have been described.(17) In our patients,screening for the latency associated nuclear antigen(LANA) and intracytoplasmic inclusions used for the diagnosis of HHV 8 couldn't be ascertained owing to the resource constraints.All our patients tested negative for HIV 1 and 2 which thus made the diagnosis of PEL as a cause of lymphoma unlikely,though the other biochemical findings were in favour of it(significantly raised fluid ADA levels).

Pyothorax associated lymphoma is seen typically in untreated cases of Tubercular effusions demonstrating the metaplasia of the pleural epithelium.However they typically present with a tumour mass in the body.(18) These findings made the diagnosis of pyothorax associated lymphoma incompatible with the clinical status of our patients.

The rationale :

In a resource and capital limited set up like that of the ours,it would be a wise decision to hasten the initiation of the standard chemotherapy regimens in patients presenting as acute polyserositis with an exudative and lymphocytic picture and supranormal fluid ADA levels.This would help the physician in preventing an early mortality and even achieving good 5 year survival rates comparable to the set ups with more advanced health logistics.

The possible paradox observed in the study : Absence of HIV in lymphoma associated pleural effusions

In the literature documented previously,majority of the lymphoma associated effusions had AIDS and rather,extranodal Burkitts and PEL have been described as AIDS defining illnesses.(2, 19-21) However with such a dictum,the status of our patients defines the level of incongruity.None of the 5 patients tested positive for HIV in our case series.The possible explanation for such an anomaly can be a possible existence of a rarer form of immunodeficiency either primary or secondary which has led to a severely immunocompromised state,thereby dysregulating the lymphocytes. However,if that is the case,why was the underlying immunodeficiency dormant for such a long time ?

If the need be,a detailed immunohistochemical,cytogenetic and viral analysis should be undertaken for arriving at diagnostic set point in dubious situations like these.

To summarise :

- Non Hodgkins lymphoma of the extra nodal Burkitts type has an alarming rise in the incidence in the developing countries.
- Presentations vary,but a high index of suspicion broadening the differentials to include NHL as temporal cause of acute onset polyserositis is the need of the hour.
- It has to be borne in mind that not every lymphocytic exudative effusion with raised fluid ADA levels is tuberculosis even in high endemic zones.
- One should be skeptical about the levels of fluid ADA in such cases and if surpassing 100IU/L,a detailed histopathological and if required,an extensive immunohistochemical and virological work up must be ordered.
- Decision to initiate empirical standard chemotherapy regimens must not await the results of immunohistochemical analysis thereby buying time.

CONCLUSION:

Even in developing countries like India where tuberculosis is omnipresent,a clinician must not get blinded away by the routine laboratory work up and rather must be a critical analyst of the obtained results.The therapy of Tuberculosis and that of Non Hodgkins lymphoma varies by wide horizons and it is ultimately the patient's life which matters.It is totally the discretion of the treating physician to follow the technical rationale which might help the patient in an immense way.

Conflicts of interest:

There are no conflicts of interest in any reference whatsoever pertaining to the work.

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