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AUTOIMMUNITY IN AN IMMUNOSUPPRESSIVE CONDITION: A CASE OF PEDIATRIC HIV WITH SYSTEMIC LUPUS ERYTHEMATOUS.

Paediatrics

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ABSTRACT

Background: Systemic Lupus Erythematosus(SLE) is a chronic autoimmune disease and its coexistence with human immunodeficiency virus (HIV) (simultaneously) has been rarely reported in literature with only 10 such reported cases, to the best of our knowledge. We report a case of an 11 year old girl with concomitant SLE and HIV infection with tuberculosis. **Clinical Description:** An 11 year old girl, newly diagnosed with HIV infection was detected to have disseminated tuberculosis (pulmonary with abdominal) radiologically. She was admitted and started on antituberculosis treatment, following which Highly active antiretroviral therapy was introduced. However, she had continuous fever spikes and joint pain along with progressively deranged renal function tests. Immunological workup was sent which revealed ANA-2+, anti dsDNA- strongly positive and antihistone antibodies- negative. The diagnosis of HIV with SLE was confirmed on basis of SLE diagnostic criteria. **Management & Outcome:** Child was started on prednisolone (1 mg/kg/day) and low dose hydroxychloroquine (HCQ). Antituberculosis treatment (ATT) was continued with Anti-retroviral therapy- abacavir/ lamivudine/dolutegravir. Renal function tests normalised in next 2 week. Child was given pyridoxine and nutritional supplements. She is on regular follow up and monitoring. **Conclusion:** HIV and SLE are two diseases with exact opposite pathogenesis. HIV is immunosuppressive, while SLE is autoimmune disease and the coexistence of both can pose a dilemma both diagnostically and therapeutically.

KEYWORDS

Autoimmunity, Human immunodeficiency virus, Systemic Lupus Erythematosus

INTRODUCTION:

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating antibodies against the body's own immune system. Childhood SLE is rare before 5 years of age and is usually diagnosed in adolescence, predominantly affecting females. Pediatric prevalence is much lower than that in adults with only 10-17% of cases being diagnosed before the age of 16 [1]

Co-existence of SLE with human immunodeficiency virus (HIV) has been rarely reported in literature with simultaneous manifestations of both diseases occurring at same time.

Both diseases involve the CD4 plus T cells and with the introduction of Highly active antiretroviral therapy (HAART), an increasing number of SLE cases in children living with HIV are being reported We report a case of an 11 year old girl presenting with concomitant SLE and HIV infection with tuberculosis.

Clinical Description:

11 year old girl, 2nd by birth order, born of non-consanguineous marriage, presented to outpatient department with complaints of fever (on/off) since the last 1 year, recurring cough with 1 episode of hemoptysis a year ago and abdominal pain in the last 2 months. She had significant weight loss over the last 6 months and decreased appetite for 4 months. There was no history of vomiting, urinary complaints or rash.

Her 26 year old elder sister was diagnosed with HIV, at the age of 14 and was on HAART. Parents died few years earlier due to chronic illness- symptoms comprising of recurrent fever, weight loss and abdominal pain. However, were not tested for HIV or diagnosed. Anthropometrically, she was severe thin with a body mass index of 9.9 kg/m2. On examination- she was vitally stable, but pale and multiple bilateral cervical lymph nodes were palpable, largest measuring 1.5*1.5cm, which were matted and non-tender. On per-abdominal examination, hepato-splenomegaly was present. Liver was 2.5cm palpable, firm, liver span of 9 cm and left lobe of liver palpable. Spleen was palpable 4 cm spleen, which was firm. Investigations are depicted in table I

She tested positive for HIV-1 with a CD4 absolute count- 250 cells/ uL and Cd4%-7%. Chest Xray was s/o hilar lymphadenopathy, however gastric lavage gene expert for acid fast bacilli was negative.

Ultrasonography Abdomen: Multiple enlarged mesenteric lymph nodes - 25*18 mm with splenomegaly and mild hepatomegaly

CT Abdomen: Multiple enlarged oval shaped homogenously enhancing lymph nodes in small bowel largest measuring 22*16 mm.

Table I: Baseline Investigations

Investigations on admission	
Hemoglobin -7.6 g/dl	Reticulocyte count- 2.0%
PCV- 24.6%	ESR- 130mm/hr
MCV- 85.1 fl	CRP- 16.9 mg/L
MCH- 26.3 pg	Serum Iron- 25.8 mcg/dl
MCHC- 30.9 g/dl	TIBC- 224mcg/dl
WBC-15,500/cumm	BUN/Creatinine- 8/0.8 mg/dl
Platelet -181lacs/cumm	Total bilirubin/Direct bilirubin- 0.5/0.2 mg/dl
BUN/Creatinine 3 days after starting HAART	
Day of admission	BUN/ Creat
19	20/1.4 mg/dl
21	21/1.5 mg/dl
Repeat complete blood count on day 19 of admission	
Hemoglobin	6.4 g/dl
Total WBC counts	4800/cumm
Platelets	292 lacs/cumm

Child was diagnosed with disseminated tuberculosis (Pulmonary and abdominal) radiologically and she was started on Antituberculosis treatment (ATT) regimen (rifampicin sensitive). 2 weeks later, HAART was started- Abacavir, Lamivudine and Dolutegravir (AL/DTG). However, intermittent abdominal pain persisted with poor appetite and continuous fever spikes with a maximum of 38.4 degree Celsius. Repeat blood tests were done which revealed deranged renal function tests. A drop in Hemoglobin was noticed in the complete blood count. (table I)

Pediatric Nephrology opinion was taken and the following investigations were done. (table II)

Child developed complaints of joint pain in both elbows and knee joints- more in the morning, not associated with any limitation of

activity, relieved by symptomatic medications. ATT induced lupus or nephritis vs Systemic Lupus Erythematosus or HIV Associated Nephropathy (HIVAN) were the differential diagnosis considered. However, tests required to confirm diagnosis were overlapping with the diagnosis of HIV. ESR could be high in HIV as well as tuberculosis, however an ESR of 130 mm/hr was suggestive of an ongoing inflammatory process. ANA could be falsely positive in HIV as well as ATT induced lupus. Likewise, DCT could be falsely positive in HIV, as well.

In light of these confounding factors leading to a diagnostic dilemma, Rheumatology opinion was taken and further investigations were done. (Table II)

Management and Outcome:
Rheumatology review was done with all investigations: - Child started on Prednisolone and low dose Hydroxychloroquine (HCQ) in view of fitting into criteria for SLE- 3 clinical criteria and 3 lab criteria. Child was then followed up bimonthly and serial renal function tests revealed a normalizing trend. RFTs improving to 1.81.3 - 1.0 0.9 . She is currently on ATT: HRZE and pyridoxine, ART: AL/DTG, Prednisolone (1mg/kg/day) and HCQ, cotrimoxazole-trimethoprim prophylaxis and nutritional supplements.

Table II: Further Work Up

Test	Report
Urine Routine and Microscopy	Protein: +1 / blood: absent pus cells: 2-3/hpf / RBC: 1-2/hpf
Urine Protein/ Creatinine Ratio	0.53 mg/mg
24 Hour Urinary Protein	246 mg/24 hours
DAT AND IAT	DAT positive
Serum Ferritin	1261 (raised) ng/ml
CRP	6.2 mg/dl
ESR	185 mm/hr
2D Echo	Normal
Anti-histone Antibodies	Negative
ANA	**2+ speckled homogenous pattern**
Anti dsDNA	**Strongly positive**
*DAT – direct antiglobulin test, IAT – Indirect antiglobulin test	

DISCUSSION:
Very few cases of pediatric HIV with SLE have been reported in literature- only 10 cases have been reported, out of which 7 cases only had lupus nephropathy as the clinical manifestation whereas the other 3 cases had other manifestations such as vasculitis and joint manifestations.[1] The co-existence of SLE along with HIV has been rarely seen probably due to the mechanism of the disease entities- SLE is a CD4 T cell mediated disease and HIV has been known to predominantly affect the CD4 T cells. However, with the introduction of HAART, increasing cases of SLE are being reported probably due to immune reconstitution .[2,3]

There is increasing evidence that viruses may play a major role in the development of many rheumatologic diseases. Epstein-Barr virus, parvovirus, hepatitis, and retroviruses are potential triggers for various rheumatic disorders, including lupus. In HIV, glycoprotein 120 (gp 120) plays an important role in immune dysregulation. It can bind to CD4 on T cells to cause T cell activation and decreased self-tolerance. It can also bind to CD4 on B cells and cause polyclonal B cell activation . It is possible that HIV infection might contribute to the development of SLE in patients such as ours. [4,5]

HIV and SLE both have various similar clinical manifestations- like fever, rash and weight loss along with laboratory investigations like anemia, leucopenia and lymphopenia. Both disorders can have significant T and B cell dysfunction with polyclonal B cell activation and T cell activation. Many patients thought to have lupus are screened for HIV for this reason. **Both diseases can have a positive ANA[6], but in HIV the titer is generally low. Anti-dsDNA antibodies are not seen in patients with HIV and are thought to be specific for lupus[4,5,7].** Complement levels are also generally normal in HIV. [4,5]

SLE is diagnosed according to the SLICC SLE criteria.(table III)

Table III: SLICC SLE criteria

Clinical criteria	Immunologic Criteria
1.Acute cutaneous lupus	***1.ANA****
2.Chronic Cutaneous lupus	***2.Anti-DNA****
3.Oral or Nasal ulcers	3.Anti Sm
4.Non scarring alopecia	4.Anti-phospholipid antibody
5.Arthritis*	5.Low complement (C3, C4, CH50)
6.Serositis	***6.Direct Coombs test****
7.Renal*	
8.Neurologic	
9.Hemolytic anemia*	
10.Leukopenia	
11.Thrombocytopenia	
Diagnosis *≥4 criteria (at least 1 clinical and 1 laboratory criteria) OR Biopsy proven lupus nephritis with positive ANA or Anti DNA*	

*** These features were present in our patient**

In our patient, other differentials for the cause of deranged renal function tests were ruled out before arriving to the diagnosis of SLE like ART induced nephrotoxicity, Drug induced lupus and HIV associated nephropathy.

The patient tested negative for anti-histone antibodies which are present in more than 95% of patients with drug induced lupus, whereas anti- dsDNA is absent in these patients. Symptoms develop after months to years of exposure in drug induced lupus and not within days of starting treatment. Drugs like Procainamide, hydralazine, quinidine, isoniazid and methyldopa among many others are known to cause drug induced lupus.[2,8,9]

HIV associated nephropathy (HIVAN) is caused by direct HIV infection of the renal epithelium and typically presents 2-5 years after the onset of disease. It is seen in patients with a CD4 count of less than 200 cells/mm3 . It is to be suspected when patient presents with nephrotic range proteinuria and rapidly declining kidney function even in the absence of edema . Kidney Biopsy is the only way to establish a diagnosis and is suggestive of dilated tubules and significant interstitial inflammation.[2,10]

ART nephrotoxicity may present with acute or chronic kidney injury or with acid-base and electrolyte disturbances . Medications like Tenofovir, Indinavir and Atazanavir are known to cause acute kidney injury. Trimethoprim- sulfamethoxazole is known to cause interstitial nephritis whereas Integrase inhibitors like dolutegravir is known to cause an increase in serum creatinine without a true decline in kidney function.

CONCLUSION:
The coexistence of autoimmunity in an immunosuppressed patient is very rare association. Diagnosis and treatment are complex, requiring a multidisciplinary approach and knowledge about the association between HIV infection and autoimmune diseases as treatment for both differ and can pose as a dilemma diagnostically as well as therapeutically.

Lessons Learnt :

1.Autoimmunity in HIV, very rare, especially at diagnosis
2.Investigations needs to be analyzed carefully for false positive as well as overlapping diseases, especially for diseases which affects immunity directly
3.Multidisciplinary approach is necessary, when disease course is not explained by single entity

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