Original Research Article

A study of clinical profile, risk factors and outcome of acute pancreatitis in HIV reactive patients in tertiary care institute

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Abstract

Nowadays the number of HIV infected persons is increasing day by day. As NACO has advised HAART to every HIV patient, so study of HAART and its toxicity has became important area of study. We have performed this observational prospective study to evaluate the cause of pancreatitis in HIV cases. In our study, 50 patients were included among which 72% cases had advanced immunosuppression. Most important etiological factor for pancreatitis in our study was NRTI based regimen (TL based,60%). The etiological profile in 32 (64%) cases was multifactorial such as NRTI and other pancreatotoxic drugs such as CPT (52%) or AKT(44%) (INH or R'cin) or OI. Most common OI causing pancreatitis was tuberculosis (44% cases). The usual causes of pancreatitis such as alcoholism, gall stones and hypercalcemia were very less.

Key Word: acute pancreatitis, HIV.

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INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas with sudden onset. The human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are worldwide public health problems. The implementation of combined antiretroviral treatment made the remission of the HIV-1 virus possible for long periods, improving the quality of life of these individuals and promoting the fall in HIV virus-related complications and deaths[1]. Notwithstanding, long-term antiretroviral drug-based treatments cause serious toxic effects. The incidence of acute pancreatitis (AP) may reach up to 40% of HIV-[2] seropositive individuals a year, which is considerably higher than for the general population, that has an incidence of 2%.[3]

METHODOLOGY

Ethics: The study began after obtaining permission from the Institutional Ethics Committee. All patients were explained the purpose and rational of the study as well as their role as participants in the study. Written informed consent was obtained from all the patients prior to enrolling them in the study.

Study design This study was observational study which was conducted in Department of General Medicine in JJ HOSPITAL, MUMBAI.

Study population: Patients with following criteria were selected for this study:- Retroviral Disease (RVD) patients with pancreatitis(acute / recurrent) admitted or on OPD basis.

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Study duration The study was conducted for two years(2015-2016) in the Department of General Medicine of Tertiary Care Hospital.

Study procedure: Following information was collected from each patient enrolled in the study, and was recorded on a Case Record Form (CRF)The patients of retroviral disease with acute and recurrent pancreatitis were studied. and detailed evaluation including history, general examination and clinical examination, investigations were performed.

Case definitions:

Inclusion criteria:- Pancreatitis will be defined as any 2 out of 3 criteria 1) Pain in abdomen ,vomiting not due to any other cause .2) Serum amylase /lipase more than 3 times of upper limit of normal.3) USG / CECT abdomen showing evidence of pancreatitis. Recurrent/chronic pancreatitis diagnosis was made based on imaging findings (CT).Classical diagnostic recurrent/chronic pancreatitis findings on CT include atrophy, dilated pancreatic duct and pancreatic calcification. Exclusion criteria –none

Data Collection: Socio-demographic data, WHO clinical staging of study population at the time of visit, CD4 count, ART data were obtained from patients admitted in medicine wards, from ART centre, from white cards available at ART centre, from green book (ART registration book) and from previous case paper records if any available . In the patients found to be having pancreatitis the antiretroviral therapy was withheld and serial lipase levels were monitored After the normalisation of serum lipase the patients were started on ABACAVIR based regimen and closely followed up and advised to report immediately if they developed vomiting / abdominal pain after introduction of new ART regimen in patients who did not tolerate reinitation of art with abacavir, were initaiated on ra;tegravir based regimen excluding nrti completely.

Investigations: Each patient's complete biochemical profile including CD4 count, haemogram including haemoglobin , total leucocyte count , platelet count, renal function tests (blood urea, serum creatinine). Serum lipase (on admission and on follow up), liver function tests including sgot and sgpt, random blood sugar,lipid profile and other infectious causes of pancreatitis. In all patients USG abdomen was done to support the diagnosis of acute pancreatitis and wherever possible CT/MRCP was done.

Introduction: Acute pancreatitis is potentially life-threatening condition that is characterised clinically by abdominal pain, nausea, vomiting, and biochemically by elevations of lipase and/or amylase. Although the annual incidence in the general population is relatively low, estimated to be 17 to 30 cases per 100 000 population[4] the annual incidence of acute pancreatitis in the patients with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) is considerably higher.[5] Pancreatitis is a well-described complication of HIV itself and its combination antiretroviral therapy. Historically, this has been predominantly associated with the usage of nucleoside reverse transcriptase inhibitors (NRTIs) such as didanosine and stavudine,[14,16] but only rarely with the usage of protease inhibitors (PIs) via the induction of hypertriglyceridemia.[6,7] Therefore, pancreatitis rate in HIV/AIDS population may have been exceedingly high because of the comorbid conditions prevalent in HIV/AIDS patients (e.g. ethanol use and biliary disease), the use of non-ART medications such as pentamidine, corticosteroids, ketoconazole, sulphonamides, metronidazole, isoniazid and opportunistic infections (e.g. cytomegalovirus, cryptosporidiosis, mycobacterial disease). [8,9,10]. In the pre-highly active antiretroviral therapy (HAART) era, the reported incidence among HIV-infected patients has been wide-ranging. One study found an incidence of 6.7 cases per 1 000 personyears (PYs) in their cohort of 939 patients followed for seven years.[11].

Nrtis and pancreatitis: Of the various combination of single and dual NRTIs that they studied, didanosine, stavudine and their combination (didanosine+stavudine) seem to be associated with particularly high rates of pancreatitis, reminiscent of high-dose didanosine monotherapy trials. In the multivariate logistic regression model, Reisler *et al*. found that of all nucleoside combinations included in the analysis, the combination of didanosine/stavudine was associated with the highest rates of pancreatitis.[12]. Coadministration of tenofovir with didanosine increases the maximum plasma concentration and area under the curve of didanosine by 48% to 64%(13),[14] . Therefore, the risk of acute pancreatitis is heightened when didanosine and tenofovir are given together. The specific mechanism of NRTI-induced pancreatitis is not yet known[15]. Mitochondrial toxicity is the common pathway of several NRTI adverse effects[9,16,17]. The clinical use of NRTI has been associated with adverse effects caused by mitochondrial dysfunction, such as acute pancreatitis, myopathy, peripheral neuropathy, anemia, neutropenia, hepatic toxicity and hyperlactataemia/lactic acidosis[18,19,20]. All NRTI have different affinities for mtDNA polymerase gamma , explaining in part the different propensity of drugs to induce toxicity , which is in the order of ddc>>ddi>d4t>>ZDV>>>TDF=3TC=FTC=ABC [20.1,20.2,20.3]

Protease Inhibitors and Pancreatitis: PI-based HAART regimens were not associated with an increased risk of pancreatitis. The severe metabolic changes in AIDS

patients may play a role In ultrastructural histologic changes found in the pancreas[21]. The hypertriglyceridemia associated with PI use is often severe and difficult to treat, and it may reasonably be expected to lead to an increased risk of hyperlipidemic pancreatitis in the HIV-infected population[22,23]. CD4 CELL COUNT AND PANCREATITIS The risk of pancreatitis is increased for the HIV/AIDS patients with lower CD4 cell counts[44].There is also evidence of an association with higher viral loads, suggesting that those with more advanced disease are at greater risk[24,25,26] There are multiple potential causes for this association: at low CD4 counts (i.e., <200 cells/mm3), HIV patients are prone to opportunistic infections, of which many have been associated with pancreatic involvement[19]. Medications for opportunistic infections prevention and treatment, including pentamidine and trimethoprim-sufamethoxazole, have also been associated with pancreatitis. Metronidazole itself could also induce acute pancreatitis[27,29]. Lastly, CD4 lymphocytes could be important in preventing the acinarcell necrosis which leads to clinical acute pancreatitis[30].

RESULTS

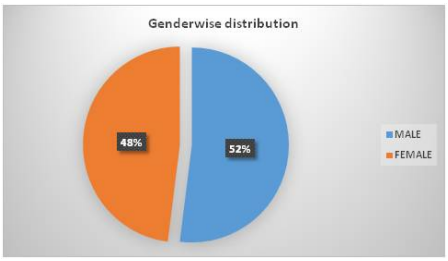


Figure 1

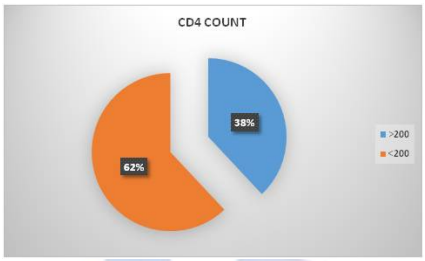
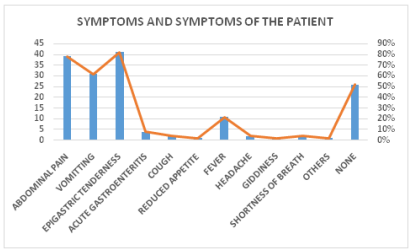


Figure 2



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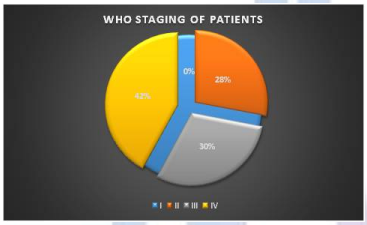

Figure 4

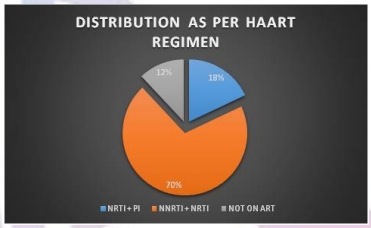

Figure 5

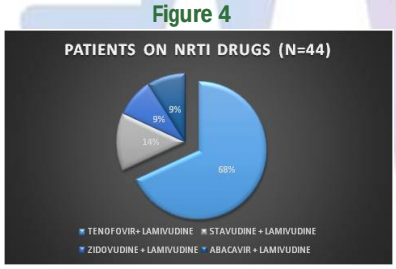

Figure 6

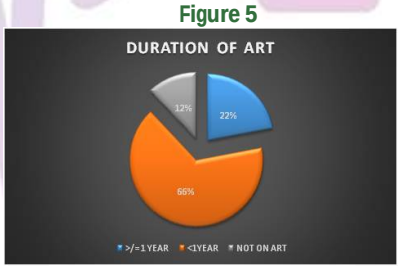

Figure 7

Table 1: Imaging findings in USG/CT

Pancreatitis	Normal	Percentage	Abnormal	Percentage	Serum lipase (>3 times upper normal. limit)
Acute (n=46)	7	15.2%	39	84.8%	46
Recurrent (n=4)	0	0	4	100%	4

Table 2: Factors Predisposing To Pancreatitis In Patients Not On Art (N=6)

Sr no	Opportunistic infection	Comorbid condition	Addiction
1	Disseminated kochs	-	-
2	None	-	-
3	Pulmonary kochs	-	-
4	None	-	-
5	Abdominal kochs	-	-
6	None	-	-

Table 3: Other Factors Which Are Implicated In Pancreatitis

AKT(INH,RIFAMPICIN)	COTRIMOXAZOLE	ALCOHOL	GALL STONES	HYPERTRIGLYCERIDEMIA	HYPERCALCEMIA
22	26	4	1	0	1

Table 4: Opportunistic Infection

Opportunistic infections	No. Of patients	Percentage (%)
Kochs	22	44
Toxoplasmosis	2	4
Candidiasis	3	6
Pcp	1	2
Cryptococcus	1	2
None	21	42

Table 5: Other Comorbid Conditions

Condition	No of patients	Percentage (%)
Renal failure	7	14
Lactic acidodis	3	6
Hbsag	2	4
Hodkin's lymphoma	1	2
Liver parenchymal disease	1	2
None	37	74

Table 6: patients with recurrent pancreatitis(n=4)

Serial Number	Art regimen On which Patient Developed Pancreatitis	Changed Regimen after Resolution of Pancreatitis	Follow up
1	TLE	ABC/L/E	RALT+ PI
2	TLATVR	ABC/L/ATVR	RALT + PI
3	ZLE	TLE	RALT + PI
4	ZLE	TLE	LOST TO FOLLOW UP

DISCUSSION

The percentage of male patients in the study were 52 % and the females 48% (Diagram 1) and the mean age was 43.5 years. Out of 50 patients 39(78%) had abdominal pain as the symptom and out of 50 patients 31 (62%) had vomiting as the symptom In 41 patients (82%) the pancreatitis was associated with epigastric tenderness as most common examination finding(diagram 2). diagram 3 shows the number of patients with advanced immunosuppression were more in our study as evidenced by 31 patients (62%) having CD4 count less than 200 and the number of patients with CD4 count more than 200 were 19(38%). Diagram 4 shows the number of patients belonging to advanced disease were more in our study. Patients with STAGE IV were 42 % while those with STAGE III were 30%, STAGE II 28 % and none of the patients belonged to stage I. From the data shown in diagram 3 and 4 it is seen that HIV patients who developed pancreatitis have advanced immunosuppresssion with low CD4 counts. Table 1.1 shows the imaging findings in our case series, 39 out of 46 patients of pancreatitis (84.8%) patients of acute pancreatitis had abnormal USG/CT findings suggestive of pancreatitis and all the 4 (100%) patients of recurrent pancreatitis had abnormal USG/CT findings . The serum lipase levels were elevated (>3 times t he upper limit of normal) in 100 % of the patients. pancreatitis. The number of patients with normal USG/CT findings were 7 out of 50 (16 %).most of the patients with acute pancreatitis had finding of bulky pancreas on USG . However none of the patients with acute pancreatitis had complications like pancreatic pseudo cyst or necrotising pancreatitis. Thus the pancreatitis is biochemical. Diagram 6 shows the no of patients on various ART regimen,9 (18 %) out of 50 patients were on NRTI + PI based therapy, 35(70%) patients were on NRTI+NNRTI based therapy and 6 (12%) patients were not on any kind of antiretroviral medications .This implied that NRTI exposure as the important causative factor for pancreatitis as all patients were exposed to NRTI. Out of 50 , 30 patients i.e 60% patients in study were on TL regimen .In the literature there are numerous case reports and studies which implicate NRTI drugs like Didanosine and Stavudine

for pancreatitis, However there is no significant data which showing pancreatitis due to TDF . However as shown in this table it can be seen that out of the 30 patients 23 were also on the other drugs like CPT and AKT(INH AND Rifampicin).This finding is of particular importance as our NACO, 1st line regimen for ART for all patients is TLE. Awareness of this particular adverse effect will lead to early and timely detection and prevent further episodes of acute pancreatitis and chronic pancreatitis. Lack of awareness of this complication leads to continuation of ART regimen by the medical officer at ART centre leading to morbidity and default of drugs. Timely diagnosis and change of regimen will lead to good compliance and prevent morbidity in patients. Diagram 7 shows that the number of patients on TENOFOVIR + LAMIVUDINE were the most in our study i.e 30 patients (68.2%) , 6 (13.8 %) patients were on STAVUDINE + LAMIVUDINE , 4 (9 %) patients each on Abacavir + Lamivudine And Zidovudine +Lamivudine . Table 1 shows thatin our study we found 6 patients with acute pancreatits who were not on antiretroviral therapy. Amongst these 3 patients were not on any medication and had no associated opportunistic infection. 1 patient had disseminated kochs, 1 patient had pulmonarykochs , 1 patient had abdominal kochs. Opportunistic infection of pancreas due to cryptosporidium, mycobacterium TB, CMV can lead to pancreatitis. However due to resource limitation it is difficult to diagnose pancreatic involvement and establish tissue diagnosis, however treating the OI may resolve pancreatitis. diagram 8 shows the duration of art**,** 11(22 %)patients were using Antiretroviral therapy since 1 year or more , 31 (66 %)participants were using Antiretroviral therapy for less than 1 year while 6 (12 %) participants were not on any antiretroviral therapy. Table 2: In our study we found that 22 patients were on anti tubercular therapy (44%) , 26 patients on cotrimoxazole (52 %) 4 patients had alcohol association (8 %) and 1 patient had hypercalcemia (2%) and none of the patients had significant hypertriglyceridemia or gall stones . Thus the causative spectrum for pancreatitis is different in HIV patients than the general population. Table3: 29 out of 50 patients had an opportunistic infection in association with pancreatitis. 22 patients (44%) had tuberculosis , 1 patient had toxoplasmosis(2%) 1 patient (2 %) had Cryptococcus infection ,1 patient (2%) had pneumocystis jerovecii infection, 3 patients (6%) had candidiasis and 21 patients (42%) had no opportunistic infection associated with pancreatitis. Thus OI can contribute to pancreatitis. Additionally the medications for treatment of OI also contribute to pancreatitis like INH and rifampicin for treatment of TB are pancreatotoxic. Sulfadiazine for toxoplasmosis also has toxicity to pancreas. Table 4: In our study 7 patients had renal failure 14 %, 3 patients had lactic acidosis (6 %) 2 patients were HbsAg positive (4%)1patient (2%) each had hodgkins lymphoma and liver parenchymal disease Table 5**:** Among the patients on -TENOFOVIR + LAMIVUDINE–Out of total 50 patients in 23 (46 %) patients the acute pancreatitis wasmultifactorial and associated with more than 1 risk factor whereas 7(14%) patients were only on TENOFOVIR + LAMIVUDINE and had no exposure to other medications/ risk factors .

1. ABACAVIR + LAMIVUDINE – out of 4 patients in 3 (6%) patients' acute pancreatitis was multifactorial.
2. STAVUDINE + LAMIVUDINE – out of 6 patients in 5(10%) patients acute pancreatitis was multifactorial, 1 patient was not on any other medication.
3. ZIDOVUDINE + LAMIVUDINE – out of 4 patients in 1 (2%) patient acute pancreatitis was multifactorial and 3 patients were not on any other medication .

Since NACO regimen for first line ART included TLE from year 2014 most of our patients were on TLE regimen as against zidovudine , stavudine and didanosine as seen in old case studies, Table 7: In 30 patients ART was changed to ABC/L/E. 3 patients died on follow up. Of the remaining 27 patients 18 patients were available for long term follow up at ourcentre while others were lost to follow up as most of them were transferred to other ART centres and all these 18 patients at 3 to 6 months follow up tolerated abacavir based regimen and did not developed recurrence of pancreatitis. table 8 2 patients had initial acute pancreatitis on Tenofovir + Lamivudine regimen.After resolution of this and normalisation of serum lipase they were substituted with Abacavir + Lamivudine based regimen .However these 2 patients developed recurrence of pancreatitis on Abacavir based regimen also and thus could not tolerate any NRTI. These patients were hence referred to SACEP panel and after detailed evaluation and consideration of multiple recurrences of pancreatitis even on Abacavir based regimen these patients were put on Raltegravir based therapy with PI combination with no NRTI. Both patients were followed up and at follow up after 6 months both of these patients had very well tolerated ART and did not have recurrence of pancreatitis. One patient had pancreatitis with Zidovudine and was substituted with Tenofovir based regimen at another ART center prior to coming to our centre. However he had recurrence with severe recurrent pancreatitis and was substituted with Abacavir based regimen. However he developed acute

pancreatitis again on Abacavir based regimen also. Hence he was referred to SACEP and the regimen was shifted to Raltegravir + PI. 4th patient had recurrence of pancreatitis after substituting with tenofovir based regimen . Initially patient had pancreatitis on Zidovudine and had recurrence on Tenfovir based. Hence ART was stopped, on follow up patients was not willing for Any ART and gave a written consent for his unwillingness for ART in view of his pancreatitis. However he was lost follow up later and hence couldn't be referred for Raltegravir based therapy after it was available from JUNE 2016. This patient developed further attacks of pancreatitis even while not on ART. He was a chronic alcoholic however he couldn't tolerate any NRTI based regimen due to additional pancreatotoxicity imposed by the ART. Thus in a patient who has other factors triggering pancreatitis additional pancreatotoxicity by NRTI may exacerbate and precipitate acute pancreatitis again. With our limited experience we found that patients who are having recurrent pancreatitis may not tolerate any NRTI as it is either precipitates attacks of pancreatitis or cause additional harm to damaged pancreas.

CONCLUSIONS

In our clinical study the most common symptom was abdominal pain and only symptomatic cases were 49 (98%) cases. 72% cases had advanced immunosuppression indicating association with pancreatitis. Most important etiological factor contributing was NRTI based regimen. Significant pancreatotoxicity with TL (60%).12 (24%) cases had no other cause to explain other than NRTI. 3 patients had no ART exposure, no opportunistic infections. In these cases pancreatitis was attributed to HIV per se. The etiological profile in 32 (64%) cases was multifactorial such as NRTI or other pancreatotoxic drugs such as CPT (52%) or AKT(44%)(INH or R'cin) and OI. The usual causes of pancreatitis like alcohol,gallstones,hypercalcemia were very less. OI were seen in 29 (58%) cases. Most common OI was tuberculosis 22 (44%), 2 (4%) had toxoplasmosis,3(6%) had candidiasis, 1(2%) had PCP. Thus OI and drugs for their treatment contributed significantly for pancreatitis.

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