Author's response to reviews

Title: Immune reconstitution inflammatory syndrome (IRIS) associated with Acquired Immuno Deficiency Syndrome (AIDS) related gastrointestinal limited Kaposi’s sarcoma presenting as Acute intestinal obstruction: A Case report & Literature review

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Author's response to reviews: see over
Resp sir,

I would like to thank the reviewers for their opinions and painstaking work. We have incorporated most of their recommendations. A point-wise summary is being included.

Regards

Ankit

Response to queries of Dr Jeff Martin

1) The first issue is whether the lesions are truly KS. The purplish lesions on the serosal surface of the small bowel look like KS, but they themselves do not appear to be responsible for the symptoms. Importantly, the “rounded cystic lesions containing dirty white fluids” in the mesentery are not, to my knowledge, typical for KS. Neither are the present of the prominent veins over the surface of these cystic lesions. This is relevant because KS is distinctly unusual in India. In fact, it is so uncommon that it has been hypothesized that Asian Indians may indeed have some protective factor against the development of KS. To resolve this issue, at a minimum, the lesion should examined for the presence of human herpesvirus 8 latency-associated nuclear antigen (LANA). A commercial stain is available for this. The lesions should also be stained for mycobacteria and fungi. In addition, would recommend that the lesion photomicrograph be examined by an experienced dermatopathologist from a center with a high volume of KS. There are several such dermatopathologists at UCSF, for example.

Response: The authors agree with Dr Martin that KS is not common in India though we are beginning to see more of KS as the no of HIV seropositive increase. At our ART clinic we currently have 4 KS patients on follow up. The lesion described was stained for Mycobacteria and Fungal stains which is a routine for our centre as Tuberculosis is widely prevalent in India. In fact fungal and mycobacterial cultures were also done due to high clinical suspicion and found to be negative. The pathologist who examined the lesion was certain regarding diagnosis.

2) The second issue is that if we assume the lesion is KS, then the question is whether it represents IRIS. It is not the case that any clinical event that occurs in the first 12 weeks after ART initiation represents IRIS. Instead, the finding may simply represent the natural progression of KS. In this case, we really cannot tell if KS in the gastrointestinal tract was present prior to ART. Specifically, we really cannot tell if the cystic lesion was present; it was not seen on the ultrasound either prior to ART or after symptoms had started. The only objective description of this case is that it might be IRIS or it might be simply natural progression of KS. It should not be described unequivocally as IRIS. If this patient has KS, the case should simply be described as an unusual manifestation of KS shortly after ART initiation.
Response: The authors agree with Dr Martin that it is difficult to be rule out natural progression but IRIS seems more likely.

3) A related issue is exactly how did the lesions cause abdominal obstruction? When I first read the abstract, I was expecting an intraluminal obstruction. Instead, the authors appear to imply that adhesions caused the obstruction. However, how were the cystic lesions related to the adhesions? Did the adhesions directly overly the cystic lesions?

Response: The cysts had adhesions to surrounding bowel loops and omentum. These adhesions were responsible for obstruction.

Response to queries of Graeme Ayton Meintjes

MAJOR COMMENTS

1) It is incorrect to state that KS-IRIS has only been reported 4 times before. I refer the authors to the following review of dermatological IRIS which describes several other cases and case series of KS-IRIS: Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin. 2006 Oct;24(4):549-70.

Response: The authors agree and changes has been incorporated.

2) In the introduction the authors state that IRIS occurs commonly in association with mycobacterial infections and lymphoma. This is incorrect. Lymphoma IRIS has been rarely reported. The common conditions associated with IRIS are mycobacterial, fungal and viral infections.

Response: The authors agree and changes has been incorporated.

3) In the introduction it is stated that KS can reactivate during HAART. The word “reactivate” is misleading. It suggests that the KS has been controlled/resolved and then recurs which was not the case. I suggest rather use the term “worsen”.

Response: The authors agree and changes has been incorporated.

4) A major issue that needs clarification is the exact cause of the bowel obstruction. In reporting the laporotomy findings the authors report that the KS cystic lesions were in the mesentry but do not suggest that these were causing luminal obstruction of the intestine. I was left with the impression that the bowel obstruction was due to the adhesions. However, in the discussion the authors state that the rapid increase in size of KS lesions caused obstruction. The authors need to clarify whether the KS cystic lesions or the adhesions were causing obstruction, throughout the paper. If it was the cystic lesions then how did they cause intestinal obstruction (extraluminal compression).
Response: The cysts had adhesions to surrounding bowel loops and omentum. These adhesions were responsible for obstruction.

5) In the discussion the authors state: “Ultrasound of abdomen was also normal which indicates that the size of KS lesion was small or it was macule.” Many would disagree with this statement. Even fairly large intestinal mass lesions can easily be missed on ultrasound. Indeed when the patient presented again with KS-IRIS the lesions were not detected on the ultrasound. This sentence should be removed.

Response: The authors agree and changes has been incorporated.

6) The authors state in the discussion: “However in this case there was a rapid increase in size of KS lesion…” This cannot be stated with certainty unless it had been shown to increase in size on imaging. Suggest state that an increase in size “probably” occurred in order to temper this statement.

Response: The authors agree and changes has been incorporated.

MINOR COMMENTS

1) In the case report provide details of the ART drugs the patient was prescribed.

Response: Provided

2) The authors state that gastritis is very common during initiation of HAART therapy. They provide no reference or evidence to support this statement. Gastro-intestinal intolerance of ART drugs is common during early ART but do they have evidence that gastritis proven on gastric biopsy is common? Provide references or delete this phrase.

Response: Gastrointestinal side-effects such as nausea, vomiting, and diarrhoea are common side effects and authors don’t mean biopsy proven gastritis. O’Brien ME et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. JAIDS 34: 407 – 414, 2003

3) Provide details of how many courses of paclitaxel the patient received and doses.

Response: Provided

4) The authors state that KS is a neoplastic disease that originates from vascular endothelium, however this is not entirely clear and most researchers in this field consider it to arise rather from lymphatic endothelial cells. See: Wood NH, Feller

Response: The authors agree and changes has been incorporated.

5) The authors state that the biliary tract is commonly involved in KS. Most would consider this a rare manifestation, can they provide data to support this?

Response


6) Suggest reword the following sentence: “Gastrointestinal KS is mostly found in the stomach and duodenum with small or large bowel being rarely involved” to rather state “Gastrointestinal KS is mostly found in the stomach and duodenum with jejunum, ileum or large bowel being rarely involved”. The duodenum is part of the small bowel.

Response: The authors agree and changes has been incorporated.

7) “Gastrointestinal obstruction has also been rarely reported.” Provide references.

Response

8) Last sentence of page 2 would better read:

“IRIS is most frequently observed in individuals with severe CD4+ T cell depletion and is believed to be due to reconstitution of immune responses to a previously existing (but clinically occult or previously treated) pathogen or tumor antigen, rather than development of new opportunistic infection or progression of opportunistic infection due to treatment failure.”
Response: The authors agree and changes has been incorporated.

9) Page 3. In summarizing case it is stated “An emergency laparotomy was done which showed matted small bowel loops with purple coloured patches on small bowel serosal surface and mesentery. “ The cystic lesions should be mentioned here too.

Response: The authors agree and changes has been incorporated.

10) first paragraph page 3. Suggest state that rise in CD4 and temporal relationship of bowel obstruction to HAART initiation also support the diagnosis of KS-IRIS.

Response: The authors agree and changes has been incorporated.

11) Not all KS-IRIS lesions need chemotherapy. A study presented at the Conference on Retroviruses and Opportunistic Infections 2009 reported KS-IRIS cases from Uganda (Martin et al, abstract 31). Cases that manifested with only skin involvement resolved with continued HAART and without chemotherapy. Suggest state that chemotherapy is indicated when KS-IRIS is severe or there is visceral involvement.

Response: The authors agree and changes has been incorporated.

12) Authors state KS-IRIS may occur in HAART naïve individuals in several places in the paper. Suggest add that it may occur in HAART naïve individuals AFTER STARTING HAART.

Response: The authors agree and changes has been incorporated.

13) On the histological specimens were there any unusually inflammatory features to suggest IRIS?

Response: None specific

14) On picture 3, the histological features should be indicated with arrows.

Should be done while proof reading.