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Title	A Retrospective Case Series of Surgically Diagnosed Idiopathic Aortitis Cases in a Canadian Centre
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Reviewer 1	Dr. Jagdish Butany
Institution	Toronto General Hospital, Pathology
General comments (author response in bold)	This paper discusses inflammatory aortic disease, in patients operated for diverse reasons. The authors have retrospectively followed the patients to see outcomes, impact of diagnosis and impact on diagnosis, of the pathology findings. The papers limitations are numbers and those those cases that they do have are over a significant period of time. The follow-up is virtually complete and that helps draw conclusions. General comments: Concise paper focused on IA. with appropriate content. Methods well defined & followed. Specific: Even if difficult, the authors must define the criteria for their major categories. **NM: this is done – definitions are added to methods section** Some illustration of the morphological entities included in this group would be helpful to the reader. **NM: I agree this is a good suggestion. I have added Figure 2 which illustrates imaging findings of one of study subjects.** Did any (if so how many) patients need re-operation for progression of disease beyond the resected ascending aorta? **NM: As discussed in the results section, 3 patients in total had additional operations during follow-up: 2 needed stents for reinforcement of the initial surgical procedure and 1 for resection of additional aneurysm (that was present on baseline imaging). So, none of the patients had surgeries because of progression of their disease.** There is no mention of any IA representing a burnt out or nearly burnt out form of other inflammatory disease. Is this term no longer tenable? **NM: This remains a valid possibility. I have added a sentence reflecting this to Introduction section.**
Reviewer 2	Dr. Cheryl Barnabe
Institution	University of Calgary, Medicine
General comments (author response in bold)	Murzin et al provide information from a retrospective cohort of patients found to have inflammation on aortic tissue pathology, and link this to clinical phenotype and treatment. As the authors introduce, idiopathic aortitis is a poorly defined entity with no criteria for diagnosis or classification, and with no treatment strategy defined. Thus, the topic is very important to the disciplines of rheumatology and cardiac surgery. Much more detail on methods for this study is required for a full assessment of the significance of the findings to be completed. **NM: the methods section is now significantly expanded.** Methods: - Can the authors provide an estimate of the completeness of case identification? Do all cardiac surgeons send the specimens to pathology for review (I'm not certain this is common practice throughout the study period) or are those specimens referred because of the clinical appearance at the time of surgery. **NM: I have added this information into the methods and the discussion sections. It is routine practice at TOH that specimen resulting from cardiac or any other significant surgeries are sent to pathology for analysis. Thus, we expect the case identification to be complete.** - Does this include autopsy specimens who present with aortic dissections too? Or only valve procedures? **NM: The pathology database we used for case identification does not contain autopsy specimen. It does however contain specimen from aortic dissections and any other surgery that yields aortic tissue performed on living patients.** - How were infectious causes excluded - did all specimens have cultures or stains completed? **NM: as is now clarified in methods section, only a subset of specimen where infectious etiology was suspected (based on clinical presentation, findings at the time of surgery or histologic evaluation) had cultures or special stains of aortic tissue.** - How many pathologists might have read these specimens, and is there an indicator for their agreement on the findings of inflammation? Any objective scales applied? More pathology description would be appreciated (types of cells present etc) **NM: Three cardiovascular pathologists, 2 of which are authors on this paper, performed histologic analyses of aortic specimen at TOH during the study period. While formal assessment of their agreement was not assessed, cases displaying unusual pathology (which includes aortitis) are frequently discussed amongst the cardiovascular pathologists so in many cases the final opinion of the report reflects opinions of more than one pathologist. No formal scale was used, but all pathologists used the definitions and classification proposed by the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology, now referenced in the paper. Although additional description of histologic findings would add valuable information, this study was mainly clinical and pathology findings (as described in pathology reports) were merely used for case identification. Providing more detailed and standardized description of pathology finding would necessitate re-evaluation of histologic specimen, which is planned for the future but has not been performed as part of this study. Furthermore, as now pointed out in the paper, the specific pattern of aortic inflammation in cases of non-infectious non-atherosclerotic aortitis has limited value for classifying the etiology of aortitis for the purpose of this study.** - For those found to have secondary aortitis in association with an inflammatory condition, how was that condition assessed/confirmed? By a rheumatologist working at that hospital only? Did you have access to community rheumatologist or internist records who may have subsequently seen the patients in consultation? **NM: You have pointed out a significant limitation of this study, and discussion of this and other limitations have now been added to the interpretation section. Because this study only looked at TOH records, only information pertaining to clinical assessments or investigations performed in TOH is available. While in one of the described cases the diagnosis of RA performed by a community rheumatologist was relayed to a TOH cardiologist which resulted in us capturing that information, the details of the diagnosis are not available to us, and it is possible that other cases had diagnoses of a systemic illness made outside of TOH that were not captured by our study.** - Did all cases have complete imaging, or only those with a secondary condition? Could the imaging have been completed in another location not linked to the Ottawa Hospital? Same with the inflammatory markers? **NM: You have pointed out a significant limitation of this study, and discussion of this and other limitations have now been added to the interpretation section. Because this study only looked at TOH records, only information pertaining to clinical assessments or investigations performed in TOH is available. While in one of the described cases the diagnosis of RA performed by a community rheumatologist was relayed to**

a TOH cardiologist which resulted in us capturing that information, the details of the diagnosis are not available to us, and it is possible that other cases had diagnoses of a systemic illness made outside of TOH that were not captured by our study.

Interpretation

- I cannot accept the estimates of incidence of non-infectious aortitis, isolated aortitis nor idiopathic aortitis - the authors present the prevalence of these diagnoses in their cohort, but this is not a population incidence by any means.

NM: We agree that the numbers we present are not representative of incidence of these conditions in the general population. Rather, these numbers represent incidence of these conditions in our population, which is population of patients undergoing cardiovascular surgery at a teaching tertiary care institution. I now added the clarification in the limitations section of "interpretation" that the conclusions of this study, including these numbers, are only generalizable to populations similar to ours. Note that we feel that these numbers represent incidence as opposed to prevalence of these conditions (in our population), because the cases were collected as they were diagnosed; we did not review histology samples performed previously (on patients who are still alive), which would be required to determine the prevalence.

- Were the authors surprised at the lack of cases in patients with ankylosing spondylitis - which is traditionally the condition associated with aortic pathology?

NM: We agree that ankylosing spondylitis is traditionally associated with aortic pathology. However, considering the overall small sample size of our sample(40 cases of non-infectious aortitis), the even smaller sample of subjects with associated systemic conditions (total 10, 8 diagnosed prior or simultaneously with diagnosis of aortitis and 2 diagnosed at f/u), and the relative rarity of ankylosing spondylitis compared to the systemic conditions found in this study (RA, giant cell arteritis, and PMR), this finding is not unexpected.

- I require further clarification on the case described as " One patient was diagnosed with RA at the time of treatment with methotrexate, 8 years after the diagnosis of IA" - did joint swelling become apparent during methotrexate therapy for IA?

NM: Thank you for pointing out this lack of clarity in describing this case. We have changed the wording (in the results section) to make the description more clear. Both the diagnosis of RA and the use of methotrexate came up during patient assessment by a TOH cardiologist. Unfortunately, no details pertaining to the diagnosis of RA are available, aside from the mention (by the TOH cardiologist) that this diagnosis was made by a community rheumatologist within the previous year, and that the methotrexate was started for that reason.

- I find it surprising that a logistic regression analysis was attempted, with so many covariates in the model. No estimates are provided (i.e. OR, 95%CI, p values) and no model fit was tested from what I can see.

NM: as suggested by the editor, we have taken the logistic regression out of the manuscript, thus we will omit addressing these concerns.

- How were cases censored for death and migration in the follow-up duration estimate? What is the median follow-up duration.

NM: As stated in the limitations session, our data was not cross-linked with administrative database, so information on vitality and migration was not available (this, we admit, is a significant limitation). The follow-up was assessed as duration between the time of surgery that resulted in histologic diagnosis of aortitis and the last follow-up recorded on TOH system (this is now clarified in the methods section). Our mean duration of follow-up was 47.5 months.

- Further description of the follow-up is needed - with only 12 patients treated a table could be created indicating what therapies were received and for how long etc - and is this information complete if medications are not accessed through the hospital? Did the patients with additional lesions or progressive lesions tend to get steroids?

NM: While we agree that a more detailed description (including a table as you have suggested) would be useful, such detailed description is not possible in our case because of lack of detailed treatment-related information (in particular the exact steroid tapering regimen and treatment stop date) on our TOH system. This is likely explained by such treatment been coordinated by specialists based outside of TOH, similar to the specific case of use of methotrexate in patient diagnosed with RA by a community rheumatologist discussed earlier. For this reason it is indeed likely that treatment-related information captured by us through TOH records is not complete, which is a significant limitation of the study (now discussed in limitations section). However, we now clarified the information pertaining to treatment in the results section to the extent that was possible. The only immunosuppressive medication that was used (in 3 subjects) in addition to corticosteroids was methotrexate. As stated in the results section and then summarized in "interpretation" section, use of steroids or methotrexate did not seem to affect outcomes such as radiographic progression in our study.

- Table 1 - high proportion of smokers - just a thought, could this be a 'Buerger's-like condition' in smokers/many CV risk factors?

NM: While we agree that a more detailed description (including a table as you have suggested) would be useful, such detailed description is not possible in our case because of lack of detailed treatment-related information (in particular the exact steroid tapering regimen and treatment stop date) on our TOH system. This is likely explained by such treatment been coordinated by specialists based outside of TOH, similar to the specific case of use of methotrexate in patient diagnosed with RA by a community rheumatologist discussed earlier. For this reason it is indeed likely that treatment-related information captured by us through TOH records is not complete, which is a significant limitation of the study (now discussed in limitations section). However, we now clarified the information pertaining to treatment in the results section to the extent that was possible. The only immunosuppressive medication that was used (in 3 subjects) in addition to corticosteroids was methotrexate. As stated in the results section and then summarized in "interpretation" section, use of steroids or methotrexate did not seem to affect outcomes such as radiographic progression in our study.

Writing:

- is Tak an accepted acronym for Takayasu's arteritis?

NM: it has been used in some reports but we agree with you that it is not "accepted," so we took it out.

- are conditions like RA and AS better characterized as inflammatory arthritis conditions rather than connective tissue disease conditions?

NM: This is a good point, we replaced the term "connective tissue disease" with "systemic inflammatory disease" which can apply to connective tissue diseases, inflammatory arthritides, and vasculitides.

- last sentence of the introduction - 'single organ vasculitis' - do you mean rather 'single location'?

NM: "Single Organ Vasculitis" is a new category of vasculitides proposed by the International Chapel Hill Consensus Conference in 2012 (proceedings paper is referenced in the manuscript). It refers to vasculitides that affect a single organ, and includes idiopathic cutaneous vasculitis, primary angiitis of the CNS, and also isolated aortitis. The definition of "isolated aortitis" we use in this paper (vasculitis that exclusively affects the aorta but not other large vessels like aortic branches) comes from this paper.

- in the second paragraph of the introduction, much more information could be presented on the findings from the Mayo Clinic and Cleveland Clinic studies - or this could be better defined in the discussion

NM: We discuss their findings further in the discussion session when we compare results of this study to theirs. While discussing those studies in further detail would most certainly be valuable, in view of the word limit and the need to significantly expand other key sections (clarifying methods, elaborating on study limitations and concluding recommendations), we were not able to add much more detail.

- The discussion could be much more sophisticated - it would be helpful to clinicians to have direction on recommendations for imaging, work-up

	and treatment. In particular, the frequency of additional lesions found with extended imaging is an important finding that should be highlighted. A recommendation on who should be treated, and the timing of new lesions being found could inform a recommendation on timing of re-imaging. **NM: We have added guarded recommendations into the discussion section, although these cannot be made with certainty. Although finding additional lesions with extended imaging is common, it is not clear whether medical treatment (such as with steroids and/or immunosuppressive agents) changes the outcome of such lesions or prevents them. Similarly, we did not find a difference in radiographic outcomes between treated and untreated subjects, which underlines the uncertainty of usefulness of treatment. Extrapolating timing of finding of additional lesions to recommendation regarding appropriate timing of follow-up imaging also would not be appropriate considering that the study is retrospective and timing of imaging was not standardized, thus the timing of finding of lesions likely has poor correlation with the timing of development of these lesions in this study. We agree, however, that recommendations such as those you suggested are very much needed, which supports our final conclusion regarding the need of systematic studies of IA.**
Reviewer 3	Dr. Daniel Yavin
Institution	University of Calgary, Division of Neurosurgery
General comments (author response in bold)	The authors have conducted a well detailed and rigorous retrospective evaluation of surgically diagnosed cases of idiopathic aortitis. The manuscript provides an informative description of the clinical features, imaging findings, and outcomes associated with this relatively uncommon condition. I expect the authors' results will be of interest to readers of CMAJ Open since likely few are already familiar with idiopathic aortitis. There were, however, several minor comments the authors could consider prior to publication. 1. The abstract refers to 684 pathologic specimens while the results section of the manuscript refers to 682 specimens. **NM: Sorry, the 682 was a typo and we fixed it.** 2. Providing an estimate of the incidence of idiopathic aortitis is one of the manuscript's key findings. It may be helpful for the authors to discuss the potential presence and magnitude of selection bias given their estimate of incidence relies on surgical specimens. **NM: We have added the discussion of selection bias and the limitation of generalizability of our results to the "interpretation" section.** 3. It would be helpful if 95% confidence intervals were reported with odds ratios since large odds ratios derived from small samples may mislead some readers. **NM: As it was strongly suggested that we remove the logistic regression analysis from this paper, we did, so this comment no longer applies.** 4. Since the incidence of idiopathic aortitis will depend in part on the pathologic criteria use to diagnose the condition, authors should include these in their methods (inflammatory infiltrates, fibrinoid necrosis, etc.). **NM: This definition is now added to the methods section of the paper. Specifically, the definitions and classification proposed by the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology, now referenced in the paper, were used by pathologists for reporting the specimen and by the study investigators to identify cases for inclusion into the study.**