Author’s response to reviews

Title: Adult ALCAPA: from histological picture to clinical features

Authors:

Hiroshi Kubota (kub@ks.kyorin-u.ac.jp)
Hidehito Endo (hendo@ks.kyorin-u.ac.jp)
Hikaru Ishii (hikaru3dg8@googlemail.com)
Hiroshi Tsuchiya (tuchinococo@yahoo.co.jp)
Yusuke Inaba (inaba178yusuke@gmail.com)
Katsunari Terakawa (terra.biz17506@gmail.com)
Yu Takahashi (alphueo@yahoo.co.jp)
Mio Noma (noma-ths@umin.ac.jp)
Kazuya Takemoto (takemotokazuya1012@yahoo.co.jp)
Seiichi Taniai (tanny0617@gmail.com)
Konomi Sakata (sakata@ks.kyorin-u.ac.jp)
Kyoko Soejima (kyokosoe3@gmail.com)
Hiroaki Shimoyamada (hshimoya@ks.kyorin-u.ac.jp)
Hiroshi Kamma (hkamma@ks.kyorin-u.ac.jp)
Hayato Kawakami (kaha@ks.kyorin-u.ac.jp)
Yukihiro Kaneko (kaneko-y@ncchd.go.jp)
Satoru Hirono (hironos@mac.com)
Daisuke Izumi (daiizumi@yahoo.co.jp)
Kazuyuki Ozaki (k-ozaki@med.niigata-u.ac.jp)
Tohru Minamino (tminamino@med.niigata-u.ac.jp)
Author’s response to reviews:

First of all, we highly appreciate to the Editor and reviewers for their consideration for our article and giving us an opportunity to re-submit the revised manuscript.

Your manuscript "Adult ALCAPA: from histological picture to clinical picture" (JCTS-D-19-00266) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in Journal of Cardiothoracic Surgery, once you have carried out some essential revisions suggested by our reviewers.

Thank you for your consideration of our article. We have revised our manuscript in response to the reviewers’ comments and are re-submitting it.

Reviewer #1:

The manuscript "Adult ALCAPA: from histological picture to clinical picture" by Dr. Kubota and colleagues is aimed at introducing two adult patients and providing from bench to bedside review of the topic. They have reported electron microscope findings that have not been discussed in human patients so far based on their knowledge of literature. While this anomaly is rare, it is quite important in cardiac surgery as its diagnosis can save the lives. Moreover, there are adult people who live with the anomaly and are prone to death mainly due to ventricular arrhythmia which is preventable by EPS measures.

The authors have mentioned details of paramedical procedures and histological diagnostics following a brief clinical history.

I would report more details about the history and clinical progress of their illness. Moreover, I would write more about the family history of the patients.

Thank you for your comment.

In response to your comment, we have added more details about the patients’ history and clinical illness in the manuscript, and we have changed the sentences as shown below:

“Case 1; The patient was a 42-year-old male with a family history of sudden early postnatal death of an elder sister whose cause of death was unknown. The patient pursued an active life without any symptoms of heart failure or arrhythmia before the sudden onset of ventricular fibrillation at 42 years of age. He had collapsed unconscious while jogging, and cardiopulmonary resuscitation (CPR) was performed by a bystander. The ambulance crew found that the patient
was in ventricular fibrillation, and they defibrillated him with an automated external defibrillator (AED). Upon arrival at the hospital, he was intubated and placed under mild induced hypothermia at 34 °C for five days. The patient gradually recovered consciousness, and was extubated. The CAG finding led to a diagnosis of adult ALCAPA (Fig. 1 A, B). A modified-Takeuchi procedure was performed, and an ICD was implanted. The patient’s postoperative course was uneventful, and as of 11.5 years after the surgical correction, he is alive and well with no complications and no ICD activations.

“Case 2: The patient was a 48-year-old male with no family history of sudden death or cardiac disease who had been told he had a systolic heart murmur since he was a child. At 42 years of age he experienced a brain infarction and developed dysarthria and left hemiplegia. An electrocardiogram after the brain infarction revealed atrial fibrillation without ischemic change. Coumadin administration was commenced, and he recovered well without sequelae and was followed up at a nearby hospital until the onset of ventricular fibrillation. Ultrasound cardiogram (UCG) two months before the onset of ventricular fibrillation showed an enlarged left ventricle (left ventricular diastolic diameter/systolic diameter: 56.4 mm/42.3 mm) and a 50.9% ejection fraction without asynergy. There was moderate mitral valve regurgitation and mild tricuspid regurgitation. Estimated right ventricular systolic pressure was 32.9 mmHg.

At 48 years of age, the patient was found unconscious in bed by his family after a quarrel. Application of an AED by a rescue team restored his heart beat. Upon arrival at the hospital, he was placed under mild hypothermia at 34oC for five days. The patient recovered consciousness without neurological deficits, and was extubated. A modified-Takeuchi procedure, mitral valvuloplasty, and maze procedure were performed (Fig. 1 C, D), and were followed by implantation of an ICD. The patient was discharged from the hospital, and he returned to work. However, nine months after being discharged he was readmitted because of mild symptoms of heart failure: facial edema and weight gain. Ultrasound cardiography at the time showed a left-to-right shunt due to baffle leakage, moderate tricuspid and mitral valve regurgitation, and pulmonary stenosis. The left ventricular diastolic diameter/systolic diameter ratio was 52.0/27.0 mm, and the ejection fraction was 58%.

Swan-Ganz catheterization revealed oxygen step-up from 58% to 67% in the pulmonary artery, a mean pulmonary capillary wedge pressure of 27 mmHg, right ventricular systolic/end-diastolic pressure ratio of 79/17 mmHg, and pulmonary artery pressure range of 55-19 (mean: 30) mmHg. Mitral valve replacement, patch enlargement of the main pulmonary artery, closure of the baffle leakage, and tricuspid annuloplasty were performed 9 months after the initial operation. Oliguria and hyperbilirubinemia developed postoperatively, and the pulmonary hypertension (50-60 mmHg) persisted. Two months later, a deep sternal surgical wound infection was detected, and sternal debridement was performed. The causative microorganism was methicillin-resistant Staphylococcus aureus. Four months later, UCG revealed multiple vegetations on the ICD lead and tricuspid ring, and the ICD generator, lead, and tricuspid ring were removed urgently. Six months postoperatively, the patient developed multiple organ failure, and after subsequently developing non-occlusive mesenteric ischemia, he died 22 months after the initial operation.”
The subtitle "clinical picture" is a little bit misleading when we are talking about diagnostic measures.

Thank you for your comment. I fully agree with you. In response to your comment, we have changed the subtitle from “from histological picture to clinical picture” to “from histological picture to clinical features.”

With regards to non-surgical therapy, they have summarized everything in one or two sentences and a single medical option (Nicorandil). My suggestion is leaving it or discuss in detail.

Thank you for your comment. I fully agree with you. In accordance with to your comment, I have deleted “e.g., nicorandil” and changed the sentence as below to the following:

“Although no standard protocol of medical control has yet been established yet, medical control with a vasodilator and anti-arrhythmic agent e.g., nicorandil may be mandatory.”

Check the references again 9 and 29 are the same. Some references are too old and can be omitted (e.g. ref 3).

Thank you for your comment.
Thank you for your comment.
In accordance with your comment, we have omitted the old references 3 and 8, and we have added some references and renumbered them.

Reviewer #2:

Dear authors,

Thank you for submitting this article to the Journal of Cardiothoracic Surgery. Put briefly, this is an exceptional article and I have no objections or suggestions for the manuscript. The research question is nicely selected and it is of great importance to have a thorough understanding of even rare cases. Authors are to be congratulated for this comprehensive approach to rare but interesting clinical entity.

Thank you for your comments. We appreciate for them.

Reviewer #3: The authors presented an interesting work, regarding two cases of ALCAPA patients. Even if from only two patients, the authors provided a complete imaging material and histological findings. However, I believe that this article requires the following major revisions:
- the authors should present the clinical history of the two patients more incisively, avoiding many elements that divert the attention (circumstances of rescue etc.) and rather focusing on: event - treatment - outcome.
- The discussion section contains a series of digressions (EPS, ICD, guidelines, outcomes etc) that goes beyond the scope of the article.

Thank you for your comments.

In response to your comments, we have deleted the description and references to the ICD implantation guideline. Because no articles have ever described an ALCAPA patient’s EPS, we would prefer to describe the EPS results as a reference for electrophysiological assessments of ALCAPA patients by cardiologists.

- The authors must focus the discussion on the histologic and imaging data: at least short hints on the specific (if any) characteristics of ischemic changes found in myocardial biopsy, in comparison of general histological findings of ischemic myocardium.

Thank you for your valuable comments.

After a discussion with pathologists focusing on the specific findings in the in biopsy specimens, I added the following sentences:

“Although the ischemic myocardial lesions associated with severe coronary atherosclerosis are generally more prominent in the subendocardial region, our cases showed chronic ischemic change not only in the subendocardial region but uniformly throughout all layers of the heart wall. Since, unlike the ischemia caused by epicardial coronary artery stenosis, the etiology of the ischemia in adult ALCAPA is a steal phenomenon, this uniform pathological ischemic change throughout all the layers may be a “specific” characteristic of adult ALCAPA.”

- The discussion section should include an "in-depth" review about the mechanisms possibly sustaining the persistent histological changes observed even after surgical correction of the case 2.

Thank you for your precise comments. In accordance with your comments, I have added the following sentences:

“Cardiac ischemia is often followed by a prolonged decrease in coronary microvascular perfusion, the so-called “no-reflow” phenomenon, even after flow in an upstream artery has been restored, and the mechanism responsible for this phenomenon involves microvascular obstruction. Myocardial fibrosis is irreversible even after restoring blood flow, but there has been little investigation of the reversibility of the thickened arteriolar walls. Hong et al. described the increased arteriolar wall thickness in an ischemic animal model of myocardial ischemia as being caused by intimal hyperplasia and a modest increase in the amorphous matrix of the wall. In their study, proliferating cells in the thickened wall stained positive with an α-actin antibody, indicating proliferation of vascular smooth muscle cells. The increased amorphous matrix and proliferated smooth muscle cells may not have been reversible even after the corrective surgery in adult ALCAPA.”
Moreover, the lack of regression of ischemic changes of the patient no. 2 should be considered also taking into account the very complicated clinical course: no general assumptions can be drawn from a single observation, and the authors should clearly state this limitation.

Thank you for your comment. We have added the following sentence:

“Since it is impossible to draw any conclusions based on only one case with a complicated clinical course, further study will be necessary.”

Minor revisions:

- What do the author mean with "degenerated myocardium"?
Thank you for your comment.
“Degenerated myocardium” means “deformity and acidophilic change of the cytoplasm, anisonucleosis, and blurriness of the striated pattern of the myocardium.”

We changed the sentence to the following:
“The LV exhibited hyalinosis, calcification, patchy fibrosis, deformity and acidophilic change of cytoplasm, anisonucleosis, and blurriness of striated pattern of the myocardium.”

- Kristensen et al. (page 10, line 15) is not referenced.
Thank you for your comment. In response to your comment, I have modified the sentence and referenced it as shown below.

“Kristensen et al. state that restoration of a dual coronary system prevents further ischemia and arrhythmias of acute ischemic origin and that the anatomical substrate for ventricular arrhythmias in patients with an old myocardial infarction is unaltered after revascularization. However, as far as we were able to determine in a review of the literature, no pathological examinations after corrective surgery of ALCAPA had ever been reported.”

- Language requires extensive revision.

Thank you for your comment. A native English reviser has revised our manuscript.