Characterisation of inflammatory response, coagulation, and radiological findings in acute Katayama syndrome: a report of three cases at the Medical University of Vienna, Austria

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Abstract

Background

Katayama fever is an acute clinical condition characterised by high fever, dry cough and general malaise occurring during early *Schistosoma spp.* infection. It is predominantly reported in travellers from non-endemic regions. Whereas the immunological response to schistosoma infection is well characterised, alterations in markers of inflammation and coagulation in response to this intravascular helminth infection are poorly understood.

Methods

Here we report the clinical, laboratory and radiological characteristics of three returning travellers suffering from Katayama syndrome. Markers of inflammation and coagulation were assessed repeatedly during follow up to characterise the host’s response to this acute helminthic infection. Radiographic findings were correlated to the clinical and laboratory markers.

Results

Clinical symptoms were suggestive for a highly inflammatory response including high fevers above 39°C, cough, and general malaise. Classical inflammation markers including blood sedimentation rate, C-reactive protein, and serum amyloid A were only moderately elevated. Marked eosinophilia (33 – 42% of white blood cells) was recorded and persisted despite anti-inflammatory and anthelminthic treatment for up to 32 weeks. Analysis of blood coagulation markers indicated substantial activation of blood coagulation reflected by elevated D-dimer (0.57 – 1.17 µg/ml) and high thrombin generation potential (peak thrombin activity: 311 – 384 nM). One patient showed particularly high levels of microparticle-associated tissue factor activity at initial presentation (1.644 pg/ml). Corresponding to the elevated markers of
inflammation, multiple opacities in liver and lungs were demonstrated in computed
tomography in one patient.

Conclusions

The characterization of the inflammatory response, blood coagulation parameters and
radiological findings in parenchymatous organs adds to our current understanding of
Katayama syndrome and serves as a starting point for further systematic investigations of the
pathophysiology of this acute helminthic infection.

Keywords

Schistosomiasis, Katayama, inflammation, coagulation, radiology, Africa
**Background**

Schistosomiasis is a debilitating chronic infection by trematode worms of the genus Schistosoma. Rural regions in the tropics are most affected leading to a global disease burden of 3-70 million disability-adjusted life years lost [1]. Humans become infected during freshwater exposure by larval stages which are shed from the snail intermediate host. Cercariae penetrate the intact skin and commence the developmental cycle in the human host developing into adult worms in the liver. Mating and migrating to the venous blood vessels of the urogenital tract (S. haematobium) or the intestinum (S. mansoni, intercalatum, japonicum, mekongi) in the human host, the adult worms and the deposed eggs ultimately lead to a variety of chronic pathologies including haematuria, haematochezia, liver fibrosis, bladder cancer, and chronic inflammation of the urogenital tract [2].

An acute clinical syndrome including high fever, cough and general malaise has been described foremost in travellers from non endemic regions exposed to schistosoma infection. This clinical condition commences 3-8 weeks after exposure and is termed “Katayama fever” or “Katayama syndrome” [3]. The clinical symptoms of Katayama syndrome are mediated by a hypersensitivity reaction to the intravascular helminth pathogens. Clinical symptoms gradually abide even without specific anthelmintic treatment and are substituted by the chronic granulomatous inflammation causing the vast majority of morbidity.

Katayama fever is an acute inflammatory reaction of the host. Whereas several studies have investigated the immunological characterisation caused by the intravascularly residing worms in animal models and the human host, little is known about the inflammatory response in human patients characterized by inflammation markers and respective radiological signs of inflammation [4]. Intriguingly, no data describing the consequences of intravascular helminth...
migration on the activation of the tightly controlled blood coagulation system in acute Katayama syndrome have been published so far. Here we report the clinical course, radiological findings, and observed alterations in markers of inflammation and blood coagulation in three returning travellers suffering from acute Katayama syndrome.
Methods

Patients were initially consulted at three distinct hospitals in Eastern Austria. Two patients were subsequently hospitalized at the Division of Infectious Diseases and Tropical Medicine at the Medical University of Vienna, and the third patient was hospitalized at a referral hospital in the province of Upper Austria. Written informed consent was obtained from patients for the provision of additional blood samples for the analysis of coagulation parameters besides routine blood draws and for the authorization to analyse clinical data. Radiological evaluation of patients was performed at the hospitals of primary consultation. The evaluation of D-dimer levels, the in-vitro thrombin generation potential and the analysis of the microparticle-associated tissue factor (MP-TF) activity was performed at the Medical University of Vienna using previously validated assays [5, 6]. Markers of inflammation were assessed using internally and externally quality controlled standard methodology. Data were captured in an electronic database and were depicted using descriptive statistics. Due to the small sample size, original data were reported and non-parametric summary measures were depicted as appropriate.
Results

Clinical characterisation of patients and radiographic findings

Two female and one male Austrian citizen aged 19 to 21 years presented at hospitals in Eastern Austria due to abrupt onset of general malaise, high fever and a productive cough. All patients returned from a four week travel to the Republic of Tanzania three weeks prior to the onset of symptoms. The journey consisted of work in a developmental aid programme in a rural community, a game park visit and freshwater exposure in Lake Malawi. Patients were treated empirically by the attending physicians of the initial health care institution with broad spectrum beta-lactam antibiotic treatment for suspicion of pneumonia. Repeated radiologic examinations were performed and the two female patients were subsequently transferred to the inpatient ward of the Department of Infectious Diseases at the Medical University of Vienna due to progressive clinical deterioration. The third patient - a young male Austrian citizen – was hospitalized at a referral hospital in the province of Upper Austria.

The clinical diagnosis of acute Katayama syndrome was established based on the available patient history, laboratory parameters and radiographic findings. Anti-inflammatory treatment with corticosteroids and concomitant anthelminthic treatment with praziquantel was administered. Patients showed rapid clinical recovery to this treatment and were discharged within 5 days. Malaria and systemic bacterial or fungal infections were excluded by repeatedly negative thick blood smears and multiple blood cultures. Clinical follow up visits were performed over a six month period. Schistosoma specific antibody titres – initially negative during the acute phase of infection – later converted to a positive result in all three patients and confirmed the initial clinical diagnosis. No egg excretion was detected during follow up in any of the patients. A second cycle of praziquantel treatment was administered 3
months after initial presentation to target previously immature stages, which are less
susceptible to praziquantel.

Chest X-ray was performed in all patients but did not show pathological alterations.
Abdominal ultrasound was performed and a slightly enlarged spleen was documented in one
case (14.4 cm diameter). Thoracic and abdominal computed tomography was performed at the
hospital of initial presentation due to the clinical diagnosis of systemic inflammatory response
syndrome in one patient. Multiple opacities in both lungs measuring up to 9 mm were
discovered (Figure 1). In addition, multiple hypodense foci were observed in the hepatic
parenchyma (Figure 2). These radiological findings were described as alterations resembling
metastatic abscesses of septic or malignant origin.

Characterisation of inflammatory response and blood coagulation parameters
Clinical and laboratory markers of inflammation were repeatedly assessed during follow up of
patients (Table 1.) All individuals experienced high fevers above 39°C at initial presentation.
Classical markers of inflammation including C-reactive protein (CRP; 6 – 23 mg/l), serum
amyloid A (SAA; 52 – 67 mg/l), and blood sedimentation rate (BSR; 27/36 – 82/110 mm/h)
were moderately elevated. Correspondingly, total leukocyte count was elevated and marked
eosinophilia ranging between 33 - 42% of white blood cells was detected in all patients.
Inflammation markers returned to normal levels rapidly after initiation of anti-inflammatory
treatment with corticosteroids. However, eosinophilia only gradually declined and persisted
for up to 32 weeks after initiation of treatment. Elevated lactate dehydrogenase (LDH) levels
were demonstrated in one patient with a particularly pronounced inflammatory response (391
U/l).
Blood coagulation parameters were assessed in the two female patients (Table 2). Here, D-dimer levels were elevated at presentation indicating activation of haemostasis and fibrinolysis (1.2 and 0.6 µg/ml, respectively) and fibrinogen levels were slightly increased (477 - 517 mg/l). The thrombin generation potential was increased at presentation as reflected by a higher peak thrombin generation (384 and 311 nM, respectively) compared to follow up measures. In one patient the peak thrombin generation was increased at the end of follow-up without evidence for disease activity. Finally, the MP-TF activity was markedly raised in one patient up to 1.644 pg/ml before gradually declining to 0.03 pg/ml.
**Discussion**

Acute Katayama fever is thought to be mediated by a systemic hypersensitivity reaction to migrating parasites and circulating immune complexes at the onset of egg production [4]. This immune response causes an inflammatory reaction leading to the classical clinical symptoms. The clinical presentation of the reported cases was indicative for such an acute and highly inflammatory response. Patients showed high fevers above 39°C and were manifestly incapacitated by the clinical disease course. Contrary to these findings, however, classical inflammation markers including CRP and BSR were only modestly elevated. At the same time eosinophilia – a hallmark of invasive helminthic infections – was markedly elevated. Interestingly, eosinophilia persisted for more than six months prior to normalisation indicating prolonged exposure to helminthic antigen stimulation. This finding may be explained by the fact that praziquantel – although administered in our patients already during acute infection – has little activity against early developmental stages of schistosomal worms and complete cure from all intravascular worms was therefore achieved only after re-administration of praziquantel during the follow up period [7].

Acute Katayama syndrome is a systemic state of inflammation and distinct radiographic abnormalities of the lungs have been described in acute Katayama syndrome in a few case reports [8-10] including patchy pulmonary infiltrates in chest X-ray [11]. Single or multiple pulmonary nodules with ground-glass halos were reported in standard X-ray or in computed tomography [12]. However, radiological alterations in other parenchymatous organs have been less well described. Computed tomography in one of our patients showed radiographic alterations of the lung interstitium concordant with previous reports. In addition, multiple hypodense foci of comparable appearance were demonstrated in liver parenchyma indicating a generalized inflammatory response during acute Katayama syndrome both in lung and liver.
tissue (Figure 1 and 2). This finding supports the hypothesis of a systemic inflammatory
response as opposed to a localized immune response in the lungs as the cause for the
respective radiological alterations. Whereas these findings are intriguing information from a
scientific point of view, the authors are convinced that computed tomography should not be
considered as a standard diagnostic examination for patients with suspected Katayama
syndrome. CT-examinations lack pathognomonic features for this disease and risks of
exposure to radiation most likely outweigh the diagnostic benefit in Katayama syndrome.

Detailed analysis of the blood coagulation system including D-dimer, which indicates an
activation of haemostasis and fibrinolysis, the thrombin generation potential, a global in-vitro
assay indicating an individual’s coagulation potential, and measurement of the MP-TF
activity, which reflect a prothrombotic state, showed considerable variability in acute
schistosomiasis. From a theoretical point of view, one may speculate that intravascular
migration of helminths may result in activation of the blood coagulation system despite the
absence of clinical consequences including thrombosis and thrombophlebitis. Concordantly,
this activation was demonstrated by increased levels of D-dimer, a high peak thrombin and a
marked increase of the MP-TF activity in one patient. This was less evident in a second
patient, which may be explained by either lower response in this patient or the fact that the
peak in alterations may have been missed due to the referral from another hospital. Despite
the intravascular localization of schistosomal worms and the pronounced activation of the
blood coagulation system, clinical complications such as thrombotic events are not commonly
reported in the context of acute schistosomiasis. A better understanding of the underlying
mechanisms for this puzzling discordance of clinical disease and laboratory findings may
prove particularly fruitful to improve our knowledge of the complex interplay between
helminth pathogens and the host’s response.
Conclusion

The characterization of the inflammatory response, activation of the blood coagulation system and description of corresponding radiographic findings in our patients may provide helpful information for the diagnostic workup of future patients with acute febrile conditions returning from the tropics. Based on these first preliminary findings, a further systematic evaluation of the impact of intravascular helminth infection on blood coagulation and the inflammatory response may be considered a particularly rewarding endeavour.
Abbreviations

MP-TF, microparticle-associated tissue factor; CRP, C-reactive protein; SAA, serum amyloid A; BSR, blood sedimentation rate; LDH, lactate dehydrogenase; CT, computed tomography; max, maximum; PCT, Procalcitonin.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HL, RG, MR collected, assembled and analyzed the data. CA analyzed, supervised and interpreted all blood coagulation parameters. FA supervised and interpreted all CT scan findings. HL, WG and MR contributed to the study design, interpretation of data, writing and revision of the article. All authors read and approved the final manuscript.

Acknowledgements

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References


### Table 1 - Clinical and laboratory markers of inflammation at initial presentation and during follow up

<table>
<thead>
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<th>Parameter</th>
<th>Patient</th>
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<th>Week 2</th>
<th>Week 6</th>
<th>Week 11</th>
<th>Week 32</th>
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<td><strong>Temperature (°C)</strong></td>
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<tr>
<td>A</td>
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<td>&lt;37</td>
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<tr>
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<td><strong>PCT (&lt;0.5 ng/ml)</strong></td>
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<td><strong>LDH (&lt;247 U/l)</strong></td>
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<td><strong>Leukocyte count (4-10 G/l)</strong></td>
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<td>2</td>
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<td>B</td>
<td>16.1</td>
<td>17.1</td>
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<td><strong>Eosinophile count (0-0.4 G/l)</strong></td>
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<td>2</td>
<td>3.1</td>
<td>1.2</td>
<td>0.4</td>
<td>0.3</td>
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<td>C</td>
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<td>-</td>
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<td><strong>Eosinophile relative (0-4%)</strong></td>
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max: maximum; BSR: blood sedimentation rate after one hour/after two hours; CRP: C-reactive protein; PCT: procalcitonin; SAA: serum amyloid A; LDH: lactate dehydrogenase.
Table 2 - Parameters of coagulation cascade at initial presentation and during follow up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 6</th>
<th>Week 11</th>
<th>Week 32</th>
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<tbody>
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<td>D-dimer (&lt;0.5 µg/ml)*</td>
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<td>0.06</td>
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<td></td>
<td>B</td>
<td>1.17</td>
<td>1.21</td>
<td></td>
<td></td>
<td>0.46</td>
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<td>Finbrinogen (180-390 mg/dl)</td>
<td>A</td>
<td>477</td>
<td>443</td>
<td>331</td>
<td>302</td>
<td>312</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>517</td>
<td>369</td>
<td>307</td>
<td>281</td>
<td>341</td>
</tr>
<tr>
<td>Peak thrombin generation (nM)</td>
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<td>311</td>
<td>-</td>
<td>190.2</td>
<td>168.8</td>
<td>121.5</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>384.4</td>
<td>-</td>
<td>201.6</td>
<td>236.5</td>
<td>506.1</td>
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<tr>
<td>MP-TF activity (pg/ml)</td>
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<td>0.0916</td>
<td>-</td>
<td>0.0487</td>
<td>0</td>
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<tr>
<td></td>
<td>B</td>
<td>1.644</td>
<td>-</td>
<td>1.101</td>
<td>0.115</td>
<td>0.033</td>
</tr>
</tbody>
</table>

* this cut-off indicates non-increased or negative D-dimer values.

MP-FT = microparticle-associated tissue factor
Figures

Figure 1 - Radiographic findings of lung computed tomography during Katayama syndrome (axial (A) and coronal (B) reconstruction).

Figure 2 - Radiographic findings of abdominal computed tomography during Katayama syndrome (axial (A) and coronal (B) reconstruction).
Additional files provided with this submission:

Additional file 1: manuscript Katayama revision 1 TRACK CHANGES.docx, 68K
http://www.biomedcentral.com/imedia/1880613053130639/supp1.docx