HIV-associated Extracranial Arterial Aneurysms: A Systematic Review

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Abstract

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) has been found to be associated with an increased risk of cardiovascular disease, and the development of arterial aneurysms in particular, intracranial aneurysms. In this review, we will review the reported HIV-associated extracranial aneurysms (HECAA) and their possible association with HIV/AIDS. We will discuss the proposed pathogenetic pathways leading to arterial aneurysms. HECAA, a subset of HIV/AIDS-associated arterial aneurysm (HAA), is more commonly seen in the adult population and in those with lower CD4+ T-cell counts and higher HIV viral loads. There also appears to be an advantage to early diagnosis of HECAA. There are viable treatment options available, as 61.4% of patients with HECAA underwent a corrective procedure. Furthermore, the mortality rate of 1.75% in HECAA was much lower when compared to HICAA.

Keywords

HIV; AIDS; aneurysm; arteriopathy; cardiovascular disease

1. Introduction

Among the human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) population, there is a growing concern for the increased occurrence of cardiovascular disease (CVD) [1]. There are many risk factors that have been attributed to increased prevalence of CVD in HIV patients. Some of these risk factors include chronic inflammation due to HIV and secondary infections, antiretroviral therapy (ART), especially the protease inhibitors, and their associated metabolic abnormalities, dysregulated immune

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system and molecular mimicry [2,3,4]. CVD in HIV patients may manifest in various forms. HIV/AIDS-associated arterial aneurysm (HAA) appears to be a distinct clinical entity in this population. We have undertaken the first systematic review of cases of HIV/AIDS-associated extracranial arterial aneurysms (HECAA). HIV-associated intracranial aneurysms (HICAA) have been reviewed elsewhere [5].

2. Methods

A detailed search for case reports of arterial aneurysms associated with HIV was completed on November 4th, 2017 by using various databases, including PubMed, Google Scholar, CINAHL, Cochrane Central and Web of Science. The keywords used for the search were “HIV, AIDS, arterial aneurysms, arteriopathy”. We excluded the cases of HICAA and included a total of 57 cases of HECAA in the study. The case reports were read in detail and the following variables were tabulated: year of publication, first author, title of the article, age of the patient, sex of the patient, past medical history, smoking history, family history, affected artery, CD4 count, HIV viral load, time frame between HIV diagnosis and presentation with HECAA, associated infections at the aneurysmal site, type of aneurysm, treatment offered and histology of the specimen. Because the information was gathered from case reports, the information about a given variable was not uniformly reported by authors.

3. Results

A total of 57 cases (Table 1) of HECAA has previously been reported, the earliest of which was reported in 1992. 86% of the cases reported a single HECAA while 14% reported more than one HECAA. 96.5% of the cases were reported in adults and 3.5% were reported in the pediatric population (<18 years). 86% of the reported cases were in males, 10% in females and 4% of the reports did not specify the sex. The mean age at presentation was 44.13 years (SD 13.61 years, Median 46 years, 25th percentile 35 years, 75th percentile 55 years), with the youngest patient being 10 years and the oldest being 71 years old. The prevalent cardiovascular (CV) risk factors were as follows: smoking 14%, hypertension 12.28%, hyperlipidemia 8.77%, drug abuse 8.77%, diabetes 1.75%, alcohol use 1.75%, coronary artery disease 1.75% and peripheral vascular disease 1.75%. Family history of aneurysms or connective tissue disorders was not reported in any of the cases. One patient (1.75%) had immune reconstitution inflammatory syndrome at the time of presentation. Thirty-eight cases reported CD4+ T-cell counts, with 36 reporting a specific number. The mean CD4 count of the 36 cases was 279.53 cells/mm$^3$ (SD 432.27, median 175, 25th percentile 70.25, 75th percentile 271.25). Among the 38 cases with reported CD4 count, 63% had a CD4 count less than 200 and 37% had a CD4 count greater than 200. The viral load was available in 20 patients, 3 reports did not give a specific number. The mean viral load was 386,651 RNA copies/ml (SD 1,396,725, 25th percentile 40, 75th percentile 61,200, highest: 5,800,000, lowest: undetectable, equated to zero). Thirty-five percent of the patients were taking antiretroviral therapy (ART). The mean time between diagnosis of HIV and presentation with HECAA was reported in 18 patients. The mean time between HIV diagnosis and presentation was 7.45 years (SD 5.91 years, median 7 years, 25th percentile 3.5 years, 75th percentile 10 years, shortest time frame 0.17 years, longest time frame 21 years). Of the 17 cases that reported the type of aneurysm, 71% were saccular, 24% were
fusiform and 5% were longish variety. 42% of the patients had a coinfection(s) at the site of the aneurysm, with *Salmonella* group of organisms being the most common bacterial infection. The elastic arteries were the most commonly affected (80%).

4. Discussion

According to the World Health Organization, approximately 36.7 million people were living with HIV/AIDS in 2015 [57]. The CDC reports 1.2 million people with HIV/AIDS live in the US [58]. Highly active antiretroviral therapy (HAART) has been shown to be an effective tool in reducing morbidity and mortality in HIV/AIDS patients [59,60]. However, recent studies have reported increased occurrence of CVD in the HIV/AIDS population. A meta-analysis revealed a higher relative risk of CVD in HIV patients compared non-HIV patients. HIV patients on HAART had a higher CVD risk compared to HIV patients not receiving HAART [1]. Protease inhibitors (PI) significantly contribute to improved outcomes in HIV patients [58,61]. However, there are growing concerns that there is an association between PI use and CVD [2]. CVD in HIV/AIDS patients manifests in a variety of ways; most of the studies displayed evidence of stroke and coronary artery disease in HIV patients. HAART-associated metabolic derangements, such as hyperlipidemia, hyperglycemia, and insulin resistance, chronic HIV infection/inflammation resulting in endothelial dysfunction, and traditional cardiovascular risk factors contribute to CVD in HIV/AIDS patients [2,3,4].

61.4% of the cases that we analyzed have reported repair, surgery, stenting or endovascular graft correction of an aneurysm. One case (1.75%) reported death due to aneurysmal rupture.

HIV arteriopathy was first described in 1987 [62]. HIV/AIDS-associated arterial aneurysm (HAA) was first reported in 1989 [63] and appears to be a distinct clinical and pathological entity [4,64]. The pathophysiology of HAA is not yet delineated. Calabrese et al. were the first to postulate the role of the HIV/HIV antigen-antigen antibody complex related arterial weakening as the cause of HAA development [62]. Lang et al. reported a case of HAA in which the arterial wall immunohistochemistry staining was negative for the glycoprotein 4, which is a subunit of the envelope protein complex of retroviruses, including HIV [65], thus ruling out the possible role of HIV/HIV antigen-antigen antibody complex in the development of HAA. However, HIV antigen eradication by the host immune system could be the cause of such negative immunohistochemical staining [64]. Bacterial infection of the arterial wall has also been attributed to the development of HAA. This is supported by positive bacterial cultures from aneurysmal specimen following excision and neutrophilic infiltrate on histology of the biopsy specimen. The immunosuppressed state in HIV leads to ineffective clearance of bacteria that may lead to mycotic aneurysms [66]. Furthermore, syphilis is clearly attributed to aneurysmal development [67]. However, it may be difficult to differentiate between the cause of the aneurysm in patients with both HIV and syphilis/mycotic aneurysms. Increased exposure to exogenous and endogenous elastases, which are a result of both HIV and secondary infections, is attributed to HIV arteriopathy development.

Fragmentation of the internal elastic lamina and medial degeneration in HIV arteriopathy may be caused by such elevated elastase activity [68]. HIV arteriopathy is associated with perivascular inflammation of the vasa vasorum. This may cause arterial wall ischemia which, in turn, may lead to arterial wall weakening and hence HIV arteriopathy [64]. HIV-
associated necrotizing vasculitis and leukocytoclastic vasculitis has been described in HIV arteriopathy [62]. Computational research suggests HIV envelope glycoproteins 41 and 120 are similar to artery-specific antigenic protein (ASAP) and matrix cell adhesion molecule-1 (MCAM-1). This molecular mimicry may result in the immune system targeting the arterial walls, which can lead to arterial wall degeneration. However, the authors attributed direct HIV infection of the fibroblasts of the arterial vessel wall to pathobiological phenomenon rather than molecular mimicry, as no substantial similarity was noted between the two epitopes [66]. Immune dysregulation in HIV patients results in oligoclonal proliferation of CD8 T-lymphocytes which secrete vascular endothelial growth factor-A (VEGF-A). VEGF-A is associated with vascular leakage and endothelial cell proliferation which are hallmarks of HIV vasculopathy. It is unclear if this mechanism is associated with the development of HAA [69]. There is no statistically significant difference of elevated calcium scores or calcium rich plaques in HIV patients when compared to controls. Such calcified plaques are attributed to traditional CV risk factors. Studies have demonstrated the association of non-calcified plaques with monocytes and macrophages markers (soluble CD 162 and soluble CD 14) [70,71], thus suggesting a possible role of immune activation in the development of atypical plaques. A higher prevalence of atypical, non-calcified, high-risk morphology plaques with low attenuation is noted in the coronaries of HIV patients. Such high risk-low attenuation plaques are eccentric and composed of a fatty core with a thin fibroatheroma cap [72,73]. It is still unclear if such plaques are prevalent in other arteries thus contributing to the pathogenesis of HIV arteriopathy. There is a growing body of evidence that shows higher arterial wall inflammation in high-risk coronary atherosclerotic plaques among HIV patients compared to controls [74]. In one case report, a patient had immune reconstruction inflammatory syndrome at the time of presentation of HAA [75]. Higher prevalence of typical cardiovascular risk factors in HIV patients, such as hypertension [71,72], diabetes, insulin resistance [76,78,79], dyslipidemia [78,80], and smoking [81] may act synergistically and lead to the development of HAA.

A majority of the cases reported in HICAA were in pediatric age group (73.77). Our review reveals that HECAA were mostly reported in adults (96.5%). In contrast to the HICAA, which were mostly multiple and fusiform [32], most of the of the HECAA were single at presentation and were saccular. The CD4 count was >200 in 18% and 29% of pediatric and adults with HICAA as compared to 37% in cases with HECAA. The management was mostly conservative in HICAA (91.1% of pediatric and 80% of adult cases), while 61.4% of HECAA had a corrective procedure. A higher mortality rate was reported in HICAA (60% in pediatric, 35.7% in adults) compared to low mortality (1.75%) of HECAA.

5. Conclusion
HECAA are mostly reported among adult males with a low CD4 count and high viral load. Elastic arteries were most commonly affected and co-infection at the site of HECAA is a common occurrence. Saccular variety is more common. HECAA are amenable to corrective procedures and carry a low mortality rate, likely attributable to early diagnosis.
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### Table 1.

Cases included in the study

| Paper                          | Number of cases |
|-------------------------------|-----------------|
| 1. Boggian et al. [6]         | 1               |
| 2. McKenzie et al. [7]        | 1               |
| 3. Kane et al. [8]            | 1               |
| 4. Wong et al. [9]            | 1               |
| 5. Chello et al. [10]         | 2               |
| 6. Rainer et al. [11]         | 1               |
| 7. Protopapas et al. [12]     | 1               |
| 8. Mirza et al. [13]          | 1               |
| 9. Silverberg et al. [14]     | 1               |
| 10. Heikkinen et al. [15]     | 2               |
| 11. Crevits et al. [16]       | 1               |
| 12. Kongsapet al. [17]        | 1               |
| 13. Javed et al. [18]         | 1               |
| 14. Testiet al. [19]          | 1               |
| 15. Di Cesare et al. [20]     | 1               |
| 16. Piffaretti et al. [21]    | 1               |
| 17. Mahadevan et al. [22]     | 1               |
| 18. Papasideris et al. [23]   | 1               |
| 19. Bellows et al. [24]       | 1               |
| 20. da Gama Dinis et al. [25] | 1               |
| 21. Munirathnam et al. [26]   | 1               |
| 22. Euringer et al. [27]      | 1               |
| 23. Patra et al. [28]         | 1               |
| 24. Ayers et al. [29]         | 1               |
| 25. Vohra et al. [30]         | 1               |
| 26. Seto et al. [31]          | 1               |
| 27. Orrapi et al. [32]        | 2               |
| Paper                          | Number of cases |
|-------------------------------|-----------------|
| Lucas et al. [33]             | 1               |
| Machado et al. [34]           | 2               |
| Gouny et al. [35]             | 3               |
| Zell et al. [36]              | 1               |
| Olmos et al. [37]             | 1               |
| Patetsios. [38]               | 1               |
| Brawley et al. [39]           | 1               |
| Corso et al. [40]             | 1               |
| Velez et al. [41]             | 1               |
| Brant-Zawadzki et al. [42]    | 1               |
| Kam et al. [43]               | 1               |
| Wang et al. [44]              | 1               |
| Rani et al. [45]              | 1               |
| Sharma et al. [46]            | 1               |
| Fielde et al. [47]            | 1               |
| Ando et al. [48]              | 1               |
| Catano et al. [49]            | 1               |
| Haenen et al. [50]            | 1               |
| Aziz et al. [51]              | 1               |
| Gunst et al. [52]             | 1               |
| Yasuda et al. [53]            | 1               |
| Tsimparis et al. [54]         | 1               |
| Blyth et al. [55]             | 1               |
| Ward et al. [56]              | 1               |