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Case Report

A man with age-related macular degeneration and pulmonary thromboembolism

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Abstract

Background and aim: By presenting a case with age-related macular degeneration (ARMD) and pulmonary thromboembolism (PTE), the relationship of these two conditions will be discussed.
Case presentation: A 70 year old man presents PTE. He had a history of ARMD of the left eye 5 years ago, but with incomplete improvement despite repeated intra-ocular avastin injections. Heparin and then warfarin therapy was prescribed for his PTE. Three months after starting warfarin, blindness of the right eye occurred. There was no sign of bleeding and warfarin overdose at this time. Investigations confirmed ARMD again. Avastin injection was taken and even during the Avastin injections, warfarin was not discontinued. Despite the intra-ocular injections, bleeding complication was not observed. With the completion of 6 months of anticoagulant therapy for PTE, warfarin was discontinued. Three months after cessation of warfarin, the patient re-presented with a new PTE. Warfarin was started and additional studies showed lower than normal levels for protein C and S.
Conclusion: This case can be sources of other study to detect some blood markers to find any correlation between hyper coagulate state and ARMD, effect of warfarin on the ARMD, and Avastin on thrombosis.

Key words: Age related macular degeneration (ARMD), pulmonary thromboembolism (PTE), coagulopathy, Avastin injection, Ocular Coherence Tomographer (OCT).

INTRODUCTION

Age-related macular degeneration (ARMD) occurs in "dry" and "wet" forms. It is a major cause of blindness in older ages (1). The etiology of ARMD is complex and its pathogenesis remains poorly understood. The main risk factors are smoking, exposure to light, and inflammation (2, 3, and 4). On the other hand coagulopathy disorders are relatively common in the general population. Ocular complications of coagulopathy disorders reflect both the high and unique vascularity of the eye. Both bleeding diathesis and hypercoagulate state can cause eye problems (5, 6, 7, 8). Several markers of homeostasis have been investigated in relation to ARMD, including factor VIIc, factor VIIIc, tissue plasminogen activator, and von Willebrand factor, but with inconclusive findings. There was also weak evidence that aspirin and antiphospholipid antibody syndrome is associated with an increased risk of ARMD (9, 10).

Intravitreal Anti-Vascular Endothelial Growth Factor (anti-VEGF) injection has been used worldwide for the treatment of ARMD and generally well tolerated (11). However, there is some evidence that links systemic VEGF inhibition to systemic adverse events, particularly systemic thromboembolic events (12). This is another item that correlates the ARMD and hyper coagulate state diseases.

As it can be seen, strong evidence of relationship between the hyper coagulation state and ARMD diseases is still not confirmed. On the other hand the safety of anti VEGF showed some discrepancy. So, here is a report of an interesting case with repeated pulmonary thromboembolism and wet type of ARMD in a 70 years old man. By introducing this case, plausible hypotheses about the relationship of coagulopathic disorders and ARMD will be discussed.

Case report

A 70 years old ambulatory well condition man, whose chief complaint was dyspnea and pleuretic chest was admitted to the our hospital . On physical examination, tachypnea, and pleuritic chest pain were identified. After initial examination, laboratory tests, and radiographic study (Figure 1, 2 and 3), a definite diagnosis of pulmonary thromboembolism (PTE) was ascertained. His medical sheet revealed an attack of left eye visual disturbance due to age related macular degeneration (ARMD) 5 years ago with incomplete improvement despite repeated intraocular Avastin injections.

Figure 1. CXR shows Hampton's hump sign due to PTE (white arrow)

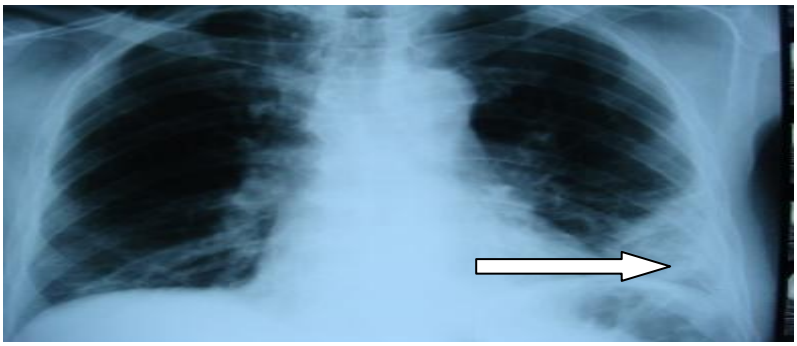


Figure 2. Lung CT shows Hampton's hump sign due to PTE (white arrow)

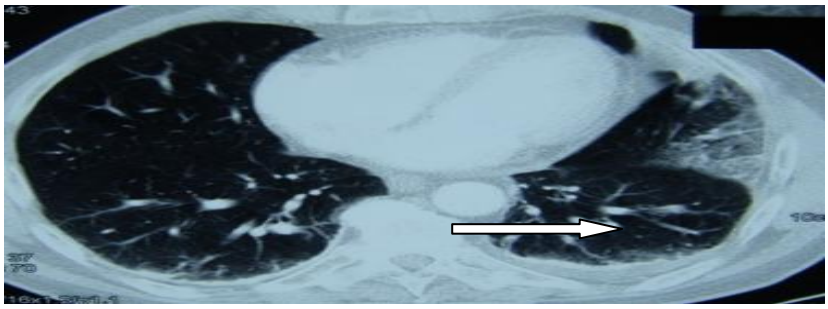
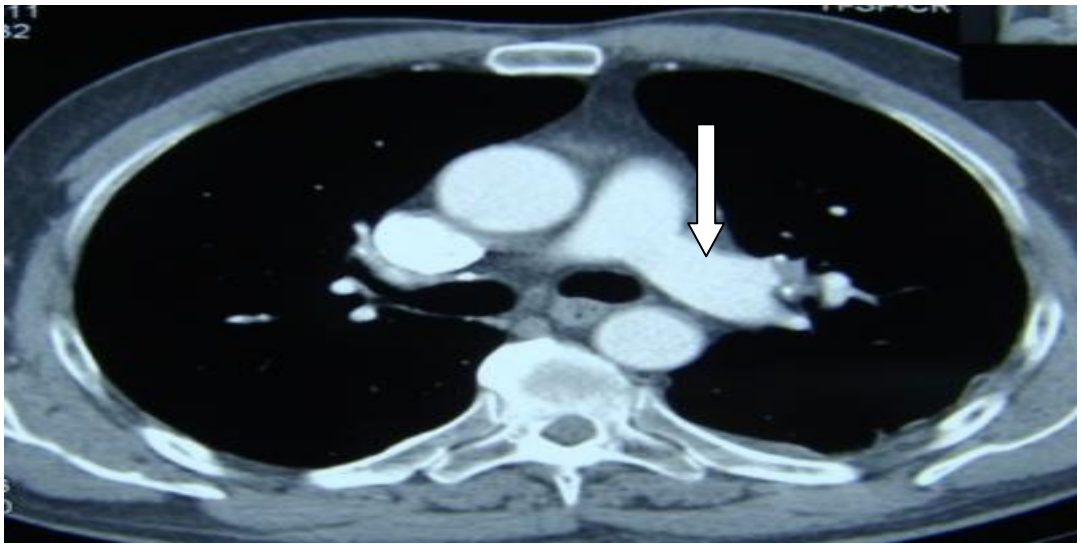


Figure 3. Pulmonary CT angiography shows intra-arterial clot in left (white arrow)



The standard treatment of pulmonary thromboembolism (heparin therapy followed with warfarin) was started. Three months after starting warfarin, an acute blindness on the right eye occurred. Coagulation tests such as PT and INR, and platelet counts were within the acceptable range and there was no sign of bleeding and warfarin overdose. The patient was referred to ophthalmologist for more evaluation. Ocular Coherence Tomographer (OCT) and angiography revealed intraretinal accumulation of fluid with an increased retinal thickness (Figure 4, 5 and 6). The findings were compatible with ARMD.

Figure 4. Fluorescent sodium angiography

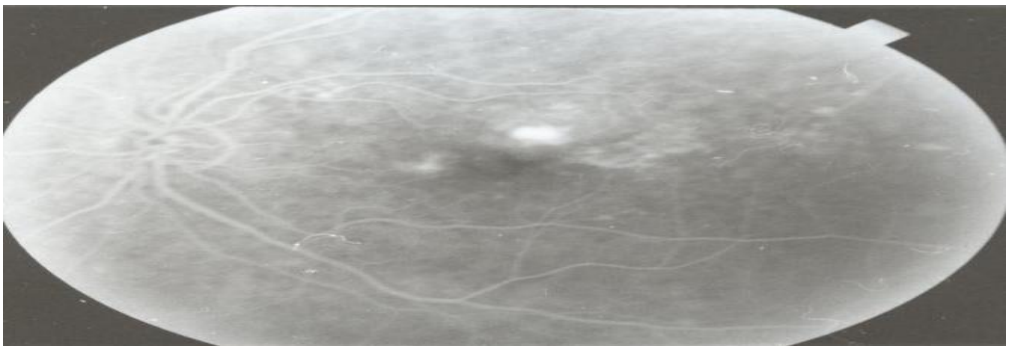


Figure 5. Optical coherent tumography

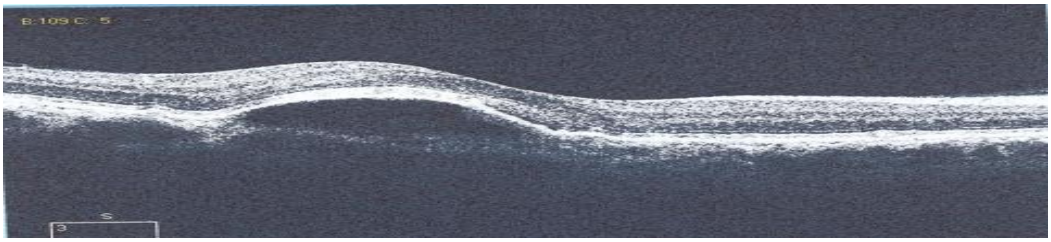
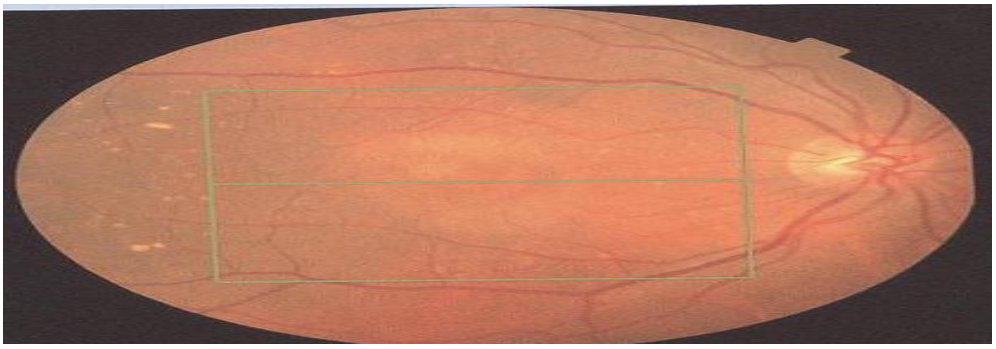


Figure 6. Fundus Photograph



A Dose of 1. 25 mg interavitreal Avastine injection was taken each month apart, for up to three months, but with not complete recovery of visual impairment. Even during the Avastin injections, warfarin was not discontinued. Despite the intra-ocular injections, bleeding complication was not observed. With the completion of 6 months of anticoagulant therapy for pulmonary thromboembolism, and complete remission of respiratory symptoms, warfarin was discontinued. Three months after cessation of warfarin, the patient re-presented respiratory symptoms and investigations revealed an occurrence of a new PTE. Warfarine was started and because of recurrent pulmonary embolism, additional studies were performed. Laboratory studies including urine analysis, blood urea, hepatic enzyme, CBC, ESR, serologic tests for vasculitis, antiphospholipid antibody syndrome and evaluations for cardiac disorders or underlying malignancies were all negative. Serum Level of Factor V liden, Factor VIII, and anti thromboine III were normal. However serum levels for factor C and Factor S were in lower than normal range.

DISCUSSION

This case was a highly sensitive report to indicate new signals in a patient who had recurrent thromboembolism and concomitant age related macular degeneration. Three Questions are been raised in this case.

The First is, is there is a relationship between hyper coagulability and age related macular degeneration? A comprehensive study has not been done in this regard. However there are some evidences that ARMD is associated with hyper coagulate state conditions. In one study 78 subject with ARMD and 25 healthy subject were enrolled and compared in terms of levels of vascular endothelial growth factor (VEGF, an index of angiogenesis), hemorheologic factors (plasma viscosity, hematocrit, white cell count, hemoglobin, platelets), fibrinogen (an index of rheology and homeostasis), and von Willebrand factor (a marker of endothelial dysfunction) . The researchers suggest an association between markers of angiogenesis (VEGF), hemorheologic factors, homeostasis, endothelial dysfunction, and ARMD (13). An elevated level of serum aCL, a risk factor for cardiovascular and cerebrovascular diseases, was also showed to be associated with exudative-type of ARMD (14).

None of these factors was present in our patient. The only hypercoagulability finding in our patients were low level for protein C and S. But these factors were measured when the patient was on warfarin. Protein C and also protein S are vitamin K-dependent protein, and its levels are reduced with warfarin administration (15). Therefore, we cannot be sure that our patient is deficient in protein C or S. Despite the lack of a clear result in our patient, probably a clotting disorder can be raised.

The Second question is, what is the effect of warfarin on age related macular degeneration. Regarding this subject, the first is whether warfarin can cause the ARMD? We reviewed the literatures on Medline about the subject; however we could not find any studies in this regard. Other medical sites were also reviewed and there was just a report on eHealthMe web site in regard of this subject. On Dec, 23, 2012: 44,335 people reported to have side effects when taking Warfarin sodium. Among them, just 88 people (0.2%) had Age-related Macular Degeneration. (http://www.ehealthme.com/). The second is whether warfarin can increase the risk of bleeding in the retina of patient with ARMD. Our patient had no such side effects during warfarin therapy, but there is evidence that all three daily antiplatelate/anticoagulant types were significantly associated with an increased risk of the development intraocular hemorrhage in patients with neovascular ARMD (16). Even for Avastin injections in our patient, warfarin had not been discontinued, and despite this, the bleeding was not observed. One retrospective chart review of patients treated with intravitreal Macugen for choroidal neovascularization resulting from ARMD while receiving warfarin therapy suggests that patients may undergo intravitreal injections safely without cessation of anticoagulation therapy (17).

The last subject of this case review is, whether Avastine can exacerbate coagulability and thrombosis. The first attack of PTE in our patient, occurred 5 years after treatment was completed with Avastin, therefore this event cannot be related to Avastin side effects. But the second attack of PTE occurred when our patient was on Avastin therapy.

Some studies have been done on the side effects of Avastin. Avastine is an anti-VEGF and has been approved for the treatment of ARMD. After intraocular injection, the Avastin enters the general circulation, suppresses plasma VEGF levels and remain in the blood for up to 8 weeks in primates, so it can have systemic side effects (18). Among these adverse effects particularly is, systemic thromboembolic events which can lead to strokes, heart disease, deep vein thrombosis and thromboembolic events (19). Since only few studies have focused on these aspects, further researches are mandatory to determine distribution and effects of these substances.

CONCLUSION

This case can be source of other study to find any correlation between hyper coagulate state and ARMD, effect of warfarin on the ARMD, and Avastin on thrombosis. Indeed one issue is to know how angiogenesis inhibitors and vascular disrupting agents upset normal homeostasis and another issue is related to inducing or preventing of ARMD by Warfarin.

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