OLGU SUNUMU CASE REPORT

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Management of a Hemorrhagic Pleural Effusion Under Apixaban Treatment in an Octogenarian Patient

Oktojenaryen Bir Hastada Apiksaban Tedavisi Altında Gelişen Hemorajik Plevral Efüzyonun Yönetimi

Derya ÖZDEN OMAYGENÇ[a],
Mehmet Onur OMAYGENÇ[b]

[a]Clinic of Anesthesiology and Reanimation, İstanbul Yedikule Chest Diseases and Chest Surgery Training and Research Hospital,
[b]Department of Cardiology, İstanbul Medipol Mega University Hospital, İstanbul, TURKEY

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Correspondence:
Mehmet Onur OMAYGENÇ
İstanbul Medipol Mega University Hospital, Department of Cardiology, İstanbul, TURKEY/TÜRKİYE
dromaygenc@hotmail.com

ABSTRACT After verification of the relevant trial data with real-world registries, it is now a widely accepted fact that Non-Vitamin K oral anticoagulants (NOACs) offer at least equal efficacy about stroke risk reduction with less bleeding events in comparison to Vitamin K antagonists. Spontaneous serous bleeding (pericardial or pleural) is a quite rare complication of NOAC treatment which had just been previously reported in a few cases with dabigatran, rivaroxaban, and apixaban. Here we present a 72-year-old patient receiving apixaban, who was diagnosed to have a massive right pleural hemorrhagic effusion during conventional heart failure treatment. Effusion was drained immediately. Reversal of anticoagulation or blood transfusion was not required.

Keywords: Anticoagulant agents; Apixaban; atrial fibrillation; hemothorax; pleural effusion

ÖZET Mevcut verilerin gerçek dünya serileriyle de desteklenmesinden sonra Non-Vitamin K oral antikoagülanların (NOAKlar), K vitamini antagonistlerine kıyasla inme riskinin azaltılmasında en az eşit etkinliği sahip olduğu ve daha az kanamaya sebep olduğu yaygın kabul gören bir gerçektir. Spontan seröz kanama (perikardiyal ya da plevral), NOAK tedavisinin oldukça nadir bir komplikasyonudur ki; daha önce dabigatran, rivaroksaban ve apiksaban ile sadece birkaç vaka bildirilmiştir. Bu bildiride, olağan kalp yetersizliği tedavisi alırken sağ taraflı belirgin hemorajik plevral efüzyon gelişen, 72 yaşında bir olgu ele alınmıştır. Olguda efüzyon hemen drene edildi ve antikoagülasyonun etkisinin kaldırılması veya transfüzyon ihtiyacı gözlenmedi.

Anahtar Kelimeler: Antikoagülan ajanlar; Apiksaban; atriyal fibrilasyon; hemotoraks; plevral efüzyon

Atrial fibrillation (AF) is the most common arrhythmia, particularly in the elderly population. Well-established association of AF with stroke occurrence, makes it into a major health problem and necessitates effective long-term anticoagulation at the expense of possible life-threatening bleeding events.[1-4] Vitamin K antagonists (VKA) had been utilized for decades to reduce the risk of thromboembolic events, but their unfavorable properties like narrow therapeutic window and drug and food interactions led to considerably high major bleeding rates (up to 6%) according to "real-world" data.[2,4-6] This problem seemed to be overcome when Non-Vitamin K oral anticoagulants (NOACs) became available for nonvalvular atrial fibrillation (NVAF) subgroup, which offer at least equal efficacy and relatively less bleeding outcome.[5,7] Apixaban -an oral factor Xa inhibitor- is a NOAC, which was proven not only to be more effective in reducing the risk of stroke as compared to VKA, but also to have a safer profile even over 75 years of age by means of decreasing the rates of total, major

and clinically relevant non-major bleeding (CRNM).[2-4,6,8,9] Bleeding into a serous cavity like pleura or pericardium is a remarkably rare complication of NOAC therapy, and thus the determination of a precise frequency is not likely. We aimed to discuss this rare condition from various aspects by reporting a case with rapidly progressing pleural effusion due to hemorrhagic conversion under apixaban treatment with a standard dosing scheme.

CASE REPORT

A 72-year-old male patient attended to out-patient clinic with heart failure decompensation symptoms. He was also previously diagnosed as permanent NVAF. He used warfarin for 2 months, however the rate of INR values in therapeutic zone was less than 20%. He had previously been evaluated for left-sided massive recurrent pleural effusion and laboratory workup including analysis of aspirated fluid did not yield a certain diagnosis other than congestive heart failure at that time. Eventually, he was treated with thoracentesis and pleurodesis. He had been taking a proper drug regimen for these medical conditions including low dose furosemide (two or three times a week) and apixaban (5 mg, b.i.d) since then. CHA_2DS_2 VASC score was 3 and the HAS-BLED score was 1.

Baseline physical examination revealed normal hemodynamic parameters, arrhythmic heart sounds, mild diastolic murmur on the left parasternal area. His initial weight was 72.3 kg. Respiratory sounds were decreased on left basal, and right basal and mid pulmonary auscultation zones and rales were heard on the left side. Lab tests were close to normal for his age group. Creatinine level was 1.2 mg/dl with an eGFR value of 58.4 ml/min. Initial chest x-ray revealed interstitial edema, right-sided pleural effusion at basal one-third of lung field, a phantom tumor and increased cardiothoracic ratio (Figure 1A). In the echocardiographic examination, mild to moderate aortic regurgitation, normal ejection fraction, mild pulmonary hypertension, and biatrial dilatation were observed. Regarding these findings, he was hospitalized and in addition to his ongoing medical treatment intravenous furosemide -with close monitorization of urine output- was initiated. Symptomatic improvement was achieved in the first two days without a deterioration in renal function tests. On the third day of treatment, a sudden-onset shortness of breath occurred. There was no respiratory sound on the right side and control chest x-ray demonstrated an outrageous increase in pleural effusion (Figure 1B). Computed tomography verified the diagnosis (Figure 1C) and emergent thoracic tube drainage was performed. The fluid was sanguineous. Apixaban treatment was immediately ceased. Since the last dose had been administered 9 hours before the event and abundant drainage was observed in the first two hours and gradually decreased, reversal of anticoagulation was not planned. Eventually, 950 ml of fluid was totally drained and further biochemical, pathological and microbiological investigation of the material did not offer an alternative diagnosis rather than hemorrhagic conversion. Clinical recovery was achieved dramatically and control chest x-ray was obtained the next day. Effusion was minimal and no additional pathology was observed in lung parenchyma except mild edema (Figure 1D). We did not observe a significant worsening in lab tests including acute phase reactants during this process. Ultimately, the patient did well after this event and could have been discharged at the end of one week. We only skipped 5 doses of anticoagulating agents and transfusion was not required within this period. Long-term anticoagulation strategy was discussed and reducing the dose (2.5 mg b.i.d) seemed reasonable. The patient was symptom-free at sixth-month visit and no bleeding event was observed henceforward. Informed consent of the patient was received for publication of clinical data.

DISCUSSION

Despite various investigations and meta-analyses concerning the safety profile, namely bleeding outcome of NOACs, have been published, regarding the rarity of the condition and equivocal classification issues, the exact incidence of pleural hemorrhage is undetermined and proper treatment recommendations do not exist. If we evaluate the entity under the heading of serous bleeding which

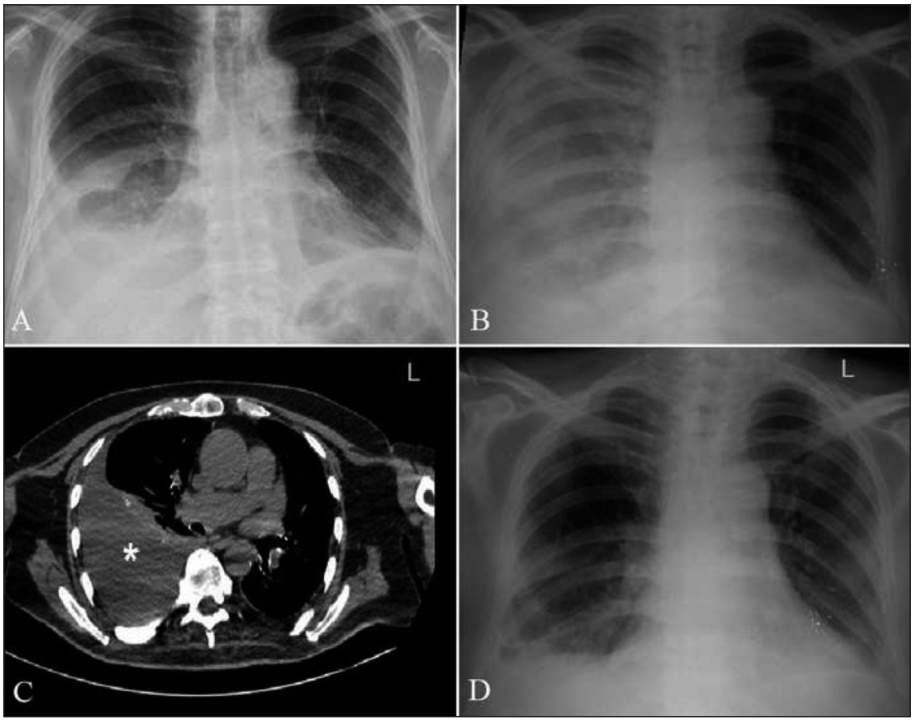

FIGURE 1: Chest X-ray of the patient on admission displaying a right-sided pleural effusion at basal one-third of lung field, a phantom tumor and increased cardio-thoracic ratio **(A)**. Repeated X-ray obtained when sudden onset shortness of breath occured. Rapidly progressed, massive pleural effusion occupying the entire lung field on the right side was observed **(B)**. CT image displaying massive right-sided pleural effusion (indicated with asterix) **(C)**. Chest X-ray obtained at the following day of drainage. Effusion was almost fully diseappeared and no additional parencyhmal abnormality except mild interstitial edema was observed **(D)**.

encompasses both pleural and pericardial hemorrhage, the data is limited to several cases and results of a meta-analysis focusing on pericardial bleeding. Individuals under VKA therapy, who were presented with massive pleural effusion had also been reported.[10-14]

Caldeira et al. reported the cumulative incidence of NOAC associated pericardial bleeding as 0.02% in their analysis embracing various phase III trials. In this publication, it was concluded that NOACs did not increase the risk of pericardial bleeding. Furthermore, there was no significant difference between agents. They also specifically emphasized that in the ARISTOTLE trial no events were pronounced during the on-treatment period.[13] Dabigatran was speculated to be the promoter of hemorrhagic pleuropericardial effusion in a case, which was associated with an intervention.[10] Apart from these, two other cases were reported with Factor Xa inhibitors. In a patient with an approximate GFR value of 30 ml/min receiving apixaban 2.5 mg twice daily, spontaneous hemopericardium and pleural effusion were observed which did not require drainage.[11] In another patient under rivaroxaban therapy, isolated hemopericardium was diagnosed. However, this patient also had a previous history of moderate chronic kidney disease and additionally a recent permanent pacemaker implantation.[12]

Pleural hemorrhage might be acceepted as a CRNM bleeding according to ISTH definitions.[15] Although major bleeding is the mainstay of safety goals in various studies, it should be denoted that CRNM bleeding might be a precursor of a more severe possibly life-threatening bleeding event. Bahit et al. underlined this reality. They declared the rate of nonmajor bleeding three times more common than major bleeding (12.1%) and found that occurrence of a nonmajor bleeding posed a remarkably higher risk for major bleeding and death. The results were favoring apixaban against warfarin in this study, but not surprisingly, bleeding into serous cavities was not identified as a separate item.[6]

Dose reduction is a controversial issue for all NOACs. Speaking of apixaban, dosage adjustment is required if the patient fulfills 2 of the following criteria: Age>80 years, Weight <60 kg, and serum creatinine level of 1.5 mg/dl or higher.[5,8] Most of the data obtained from literature advocates the safety of low dose regimen when indicated, without a significant compromise of efficacy even in the elderly population.[2-4] The only report contradicting this statement was published by Yao et al. They claimed that reduction of dosage except renal indication was associated with higher risk of stroke but a similar risk of major bleeding.[1] Our patient had an acceptable GFR value and not worsened over time. Remaining two criteria were not met either. However, concerning both the possible future bleeding events and stroke risk due to discontinuation, dose reduction deemed appropriate for long-term treatment.

To the best of our knowledge, this is the first report presenting an actual hemorrhagic transfusion of pleural effusion under apixaban treatment with proper dosing scheme. Fortunately, the diagnosis was established immediately and drainage and conservative treatment were adequate for management of the situation.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Derya Özden Omaygenç, Mehmet Onur Omaygenç;* ***Design:*** *Derya Özden Omaygenç;* ***Control/Supervision:*** *Mehmet Onur Omaygenç;* ***Data Collection and/or Processing:*** *Mehmet Onur Omaygenç;* ***Analysis and/or Interpretation:*** *Derya Özden Omaygenç, Mehmet Onur Omaygenç;* ***Literature Review:*** *Derya Özden Omaygenç;* ***Writing the Article:*** *Derya Özden Omaygenç, Mehmet Onur Omaygenç;* ***Critical Review:*** *Mehmet Onur Omaygenç;* ***Materials:*** *Derya Özden Omaygenç, Mehmet Onur Omaygenç.*

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