Massive pulmonary embolism in rheumatoid patient treated with raloxifene: a case report

Hala M. Haider

Physical Medicine, Rehabilitation and Rheumatology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Hala M. Haider, MD, Physical Medicine, Rehabilitation and Rheumatology Department, Faculty of Medicine, Ain Shams University, Egypt
Tel: +20 106 863 7029;
e-mail: hala_haider@yahoo.com

Received 2 September 2013
Accepted 15 October 2013

Egyptian Rheumatology & Rehabilitation
2014, 41:34–36

Introduction
Rheumatoid arthritis (RA) is not generally considered a risk factor for venous thromboembolism.
Case presentation
A patient with RA and postmenopausal osteoporosis was reported with massive pulmonary embolism following treatment with raloxifene for 3 months. This patient met the American College of Rheumatology (ACR) criteria for RA diagnosis in 1988. She was controlled on regular disease modifying antirheumatic drug (DMARDs) for 4 years.
Conclusion
Pulmonary embolism in postmenopausal osteoporotic patient with RA could be due to raloxifene treatment rather than a complication of the disease itself.

Keywords:
pulmonary embolism, raloxifene, rheumatoid arthritis

Egypt Rheumatol Rehabil 41:34–36

1110-161X

Introduction

Rheumatoid arthritis (RA) is not generally considered to be a risk factor for venous thromboembolism (VTE), although abnormalities of coagulation factors have been found in patients with RA. Sparse data in few patients suggest that patients with RA may have higher rates of VTE [1,2].

Matta *et al*. [2] suggested that RA is a risk factor for VTE in hospitalized medical patients. The incidence of deep venous thrombosis (DVT) following total knee arthroplasty was significantly lower in RA patients than in those with osteoarthritis. However, when patients were matched for age and NSAID use, the incidence of DVT was equivalent in the two groups [3].

However, an increased risk for pulmonary embolism (PE) and DVT was suggested in RA, supporting increased monitoring of VTE complications and risk factors, irrespective of hospitalization in a population-based study in the UK in 2012 [4].

Case presentation

Written informed consent was obtained from patient's son for publication of this case report. According to the hospital ethical committee in Kingdom of Saudi Arabia, there was approval for submission to biomedical journals.

A female Saudi patient who was 64 years of age had RA for 4 years. RA was diagnosed according to the American College of Rheumatology (ACR) criteria in 1988 [1]. She was osteoporotic as the *T*-score of lumbar dual-energy X-ray absorptiometry was -2.8, and she was menopausal for 2 years. Bisphosphonate 70 mg/week was given for 6 months, and then it was discontinued because of renal affection. Selective estrogen modulator (raloxifene) 60 mg tablet once daily was given to her, besides methotrexate 15 mg tablets/week, folic acid, and naproxen 500 mg twice daily. After 3 months, in September 2009, she was admitted to the hospital with complaints of acute chest pain in the absence of lower limb swelling. There was no joint pain or morning stiffness and no history of diabetes mellitus, hypertension, cardiac disease, or previous surgery that necessitated her being bedridden. She was not a smoker or alcoholic.

On examination, there was mild tenderness in the joints of hands and wrists, with no joint swelling. BMI was 32.8 kg/m^2. Disease activity score 28 [5] was 2.3. Laboratory results revealed anemia; hemoglobin (Hb) level was 9.8 mg/dl, white blood cell count was 10.9 × 10^6/ml, PO_2 was 135.4 mmHg, partial thromboplastin time was 88.3 s that increased to 101 s after 2 days, erythrocyte sedimentation rate was 81 mm/h, and C-reactive protein was 65 mg/l. Anticardiolipins such as IgG and IgM were negative. Serum creatinine and liver enzymes were within normal range. Venous duplex for lower limbs was negative for DVT. Chest radiographs showed left basal patchy opacities, veiling of left costophrenic angle zone, and prominent hilar vasculature with bronchovascular markings (Fig. 1). Computed tomography of chest with contrast revealed bilateral pulmonary artery embolism caused by a prominent thrombus occluding both left

and right pulmonary artery lumen that extended to all pulmonary arteries of both lower lung zone with basal pulmonary infarction (Fig. 2). There was slight left pleural effusion. Raloxifene and oral methotrexate were discontinued. She received heparin IVI, and then oral anticoagulant and oral steroid were continued.

On follow-up, oral anticoagulant was discontinued after 1 year. She complained of hand arthritis and morning stiffness for 1 h. Rheumatoid activity was 3.2 according to Disease activity score 28. When she returned back to methotrexate 15 mg/week, 5 mg prednisone daily, and naproxen 500 mg twice daily, arthritis and morning stiffness disappeared after 6 months.

Discussion

High risk for osteoporosis in people with RA is caused by disease activity, medication effects, physical inactivity, and standard risk factors such as postmenopausal status and increased age. Some studies recommended either estrogen replacement therapy or selective estrogen receptor modulator for osteoporosis in RA because of high potential of erosive esophagitis and other gastrointestinal disorders with the use of alendronate [6].

To our patient, bisphosphonate was given for 6 months before raloxifene, then it was discontinued because of multiple renal stones as seen on abdominal ultrasound and reduced glomerular filtration rate as seen on screen, which was 55%, and dual-energy X-ray absorptiometry on lumbar was -2.8.

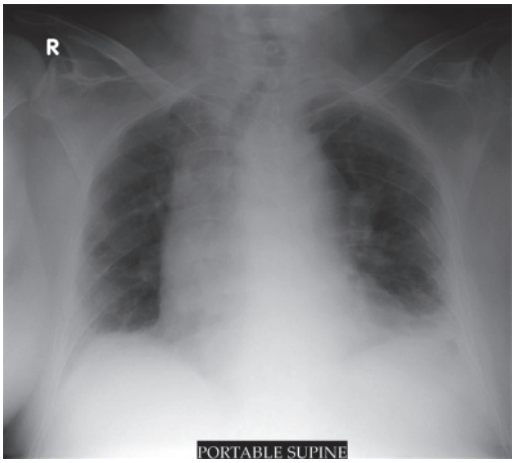
In a cohort study in Denmark between 1996 and 2006 that was published in 2010, alendronate and raloxifene carried the same risk for DVT/PE. They also observed that the risk was inversely associated with dose of both medications – that is, the risk for DVT/PE decreased with increasing average daily dose. They concluded that bisphosphonate seems to be associated with an increased risk for DVT/PE. However, the association did not seem to be causal [7].

In a certain meta-analysis study, Adomaityte *et al.* [8] concluded that raloxifene increased the risk for DVT and PE in postmenopausal women. Mosca *et al.* [9] found that, in postmenopausal women at increased risk for coronary events, the incidence of VTE and fatal stroke but not all strokes was higher in those assigned raloxifene versus placebo.

Raloxifene among different selective estrogen receptor modulators failed to significantly lower the risk for coronary artery disease in postmenopausal osteoporotic women, without any effect on stroke or early harm but doubling the risk for VTE [10].

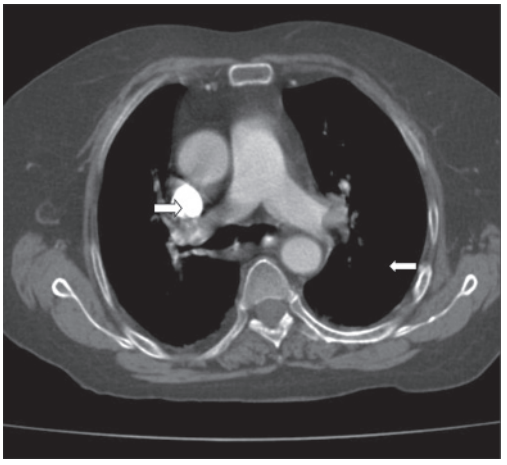
However, another study in 2005 [11] monitored the safety of raloxifene in cohort (n = 13 987) osteoporotic patients. They found that the commonest adverse reactions associated with initiating treatment included flushing, malaise, headache, migraine, nausea, vomiting, sweating, cramp, dizziness, diarrhea, mastalgia, and vaginal hemorrhage. DVT and PE were less common (n = 26). They concluded that raloxifene was generally well tolerated when used in general practice in the UK. This study concentrated on the tolerance of raloxifene and on some patients recorded with VTE, which is in agreement with our patient, as they recommended further investigation for VTE reports.

Figure 1



Posteroanterior view of plain chest radiography showed left basal patchy opacities and veiling of left costophrenic angle.

Figure 2



Computed tomography of chest showed bilateral pulmonary artery embolism caused by prominent thrombus occluding all left and right pulmonary artery lumens and extended to all pulmonary arteries of both lung zone with basal pulmonary infarction.

Ramagopalan *et al.* [12] found that people who are admitted to hospital with immune-mediated diseases (such as systemic lupus erythematosus, RA, Sjögren syndrome, psoriasis, polyarteritis nodosa, myasthenia gravis, multiple sclerosis, chronic active hepatitis, dermatomyositis/polymyositis, autoimmune hemolytic anemia, diabetes mellitus, and myxedema) may be at increased risk for subsequent VTE. They analyzed database of linked statistical records of hospital admission and death certificates for the Oxford Record Linkage Study area (ORLS) (ORLS: 1968–1998 and ORLS: 1999–2008 and the whole of UK from 1999 to 2008).

Yoshitaka *et al.* [13] found that RA was not a significant risk factor of DVT/PE in comparison with osteoarthritis (OA). They prospectively evaluated the disease-specific features of the early postoperative plasma D-dimer value and the relationship with DVT and/or PE in RA in patients following total knee arthroplasty.

In another interesting study, three patients with RA, psoriatic arthritis, and another seronegative inflammatory arthritis who were treated with etanercept developed DVT and/or PE 1–3 years after the initiation of therapy. All patients had prolonged activated partial thromboplastin time with a positive lupus anticoagulant that resisted even after 12 weeks. They concluded that, although the clinical significance of antiphospholipid antibodies during treatment with antitumor necrosis factor agents remains unclear, they may predispose patients to develop antiphospholipid syndrome when associated with prolonged activated partial thromboplastin time, lupus anticoagulant positivity, or the presence of anti-β2 glycoprotein [14].

Our patient had mild RA and was treated with methotrexate along the disease duration of 4 years. When she presented with PE, anticardiolipins were negative until 1 year of follow-up. As PE occurred after 3 months of raloxifene treatment without DVT, history of cardiac disease, or previous surgery, this massive PE is suggested to be a complication of raloxifene.

In conclusion, PE in postmenopausal osteoporotic patient with RA could be due to raloxifene treatment rather than a complication of the disease itself.

Further investigations are recommended to study the pathogenesis of thromboembolic manifestations in RA.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Arnett FC, Edworthy SM, Bloch DA, Mc Shane DJ, Fries JF, Cooper NS *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; **31**:315–324.

2 Matta F, Singala R, Yaekoub AY, Najjar R, Stein PD. Risk of venous thromboembolism with RA. Thromb Haemost 2009; **101**:134–138.

3 Niki Y, Mastumoto H, Hakozaki A, Mochizukit T, Momohara S. Rheumatoid arthritis: a risk factor for deep venous thrombosis after total knee arthroplasty? Comparative study with osteoarthritis. J Orthop Sci 2010; **15**:57–63.

4 Choi HK, Rho YH, Zhu Y, Cea-Soriano L, Avina-Zubieta JA, Zhang Y. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. Ann Rheum Dis 2013; **72:**1182–7. *doi: 10.1136*

5 Prevoo M, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; **38**:44–48.

6 Sewell K, Schein JR. Osteoporosis therapies for RA patients: minimizing gastrointestinal side effects. Semin Arthritis Rheum 2001; **30**:288–297.

7 Vestergaard P, Schwartz K, Pinholt EM, Rejnmark L, Mosekilde L. Use of bisphosphonate & raloxifene and risk of deep venous thrombosis & pulmonary embolism. Osteoporos Int 2010; **21**:1591–1597.

8 Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta- analysis. Thromb Haemost 2008; **99**:338–342.

9 Mosca L, Grady D, Barrett-Connor E, Collins P, Wenger N, Abramson BL *et al.* Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke 2009; **40**:147–155.

10 De Villiers TJ. Clinical issues regarding cardiovascular disease and selective estrogen receptor modulators in postmenopausal women. Climacteric 2009; **12**:108–111.

11 Layton D, Clarke A, Wilton LV, Shakir SA. Safety profile of raloxifene as used in general practice in England: results of prescription-event monitoring study. Osteoporos Int. 2005; **16**:490–500.

12 Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune disease: record linkage study. BMC Med 2011; **9**:1.

13 Yoshitaka T, Abe N, Minaqawa H, Date H, Sakoma Y, Nishida K *et al.* Disease-specific screening for deep venous thrombosis and pulmonary thromboembolism using plasma D-dimer values after total knee arthroplasty. Mod Rheumatol. 2008; **18**:359–365.

14 Makol A, Grover M, Guggenheim C, Hassouna H Etanercept and venous thromboembolism: a case series. J Med Case Rep2010; **15**:4–12.