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Vascular Thrombosis in Patients on Chronic Maintenance Haemodialysis Using Indwelling Venous Catheters: Case Reports and Literature Review

Samuel Kabinga[a*], Seth Mcligeyo[b], Joshua Kayima[c], Benjamin Wambugu[d], John Ngigi[e], Reuben Chege[f], John Mutiso[g]

[a,b,c,g]*University of Nairobi, East African Kidney Institute. P.O. Box 30197 -00100 Nairobi, Kenya*

[d,e,f]*Kenyatta National Hospital, Department of Medicine, P.O. Box 20723 -00202 Nairobi, Kenya*

[b]*Email: mcligeyo@yahoo.com,* [c]*Email: joshuakayima@yahoo.com,* [d]*Email: marangawambugu@gmail.com*

[e]*Email: drngigi@yahoo.com,* [f]*Email: reukiche@yahoo.co.uk,* [g]*Email: johnkmutiso@gmail.com*

Abstract

Vascular access is key in patients with end stage renal disease on maintenance haemodialysis. Thrombosis is a significant contributor of access – associated morbidity. There are several documented risk factors that predispose to thrombosis in patients with end stage renal disease. These include: inflammation, erythropoietin therapy, hypotension, diabetes and old age among others. Treatment of thrombosis in these patients is challenging. We present three cases of acute vascular thrombosis attended to in the Kenyatta National Hospital, Nairobi-Kenya, East Africa, renal department in one week and literature review.

Keywords: Vascular thrombosis; Haemodialysis catheter; endstage renal disease.

1. Cases Reports

1.1 Case number 1

B. N., a 24 year-old female, was referred to Kenyatta National Hospital (KNH) renal clinic in October 2014 with a diagnosis of hypertensive nephropathy for one year.

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* Corresponding author.

She had been using nifedipine 40 mg twice daily and atenolol 50 mg once daily with regular medical follow up. She had stable kidney function at chronic kidney disease (CKD) stage 4 for about 2 years, which deteriorated rapidly after the second year necessitating commencement of haemodialysis using a tunneled catheter in the right internal jugular vein. The catheter malfunctioned within 2 months and another one was re-inserted in the same right internal jugular vein which she used upto July 2017. She had arteriovenous fistula created in June 2017. In July 2017 she presented with symptoms consistent with superior venacava syndrome of acute onset. Investigations which included Doppler ultrasound scan of the neck vessels revealed bilateral thrombi in the internal jugular veins with extension to the right subclavian vein (Figure 1). She was admitted and commenced on unfractionated heparin 10,000 units intravenously thrice daily and warfarin 5mg once daily, with regular monitoring of International Normarized Ratio/Prothrombin Time Index (INR/PTI). An acute right femoral dialysis catheter was placed to continue with regular dialysis as the arteriovenous fistula had not matured. The tunneled catheter was not removed immediately, to allow attainment of therapeautic INR. By day 3, B.N reported to have mild epistaxis. Unfractionated heparin was stopped and she was started on enoxaparin 40mg subcutaneously twice daily. Serial INR/PTI assays were 1.36/74% at presentation, 2.76/41.7% three days after initiation of anticoagulation, and 2.49/40.2% three weeks later when the tunneled catheter was removed.

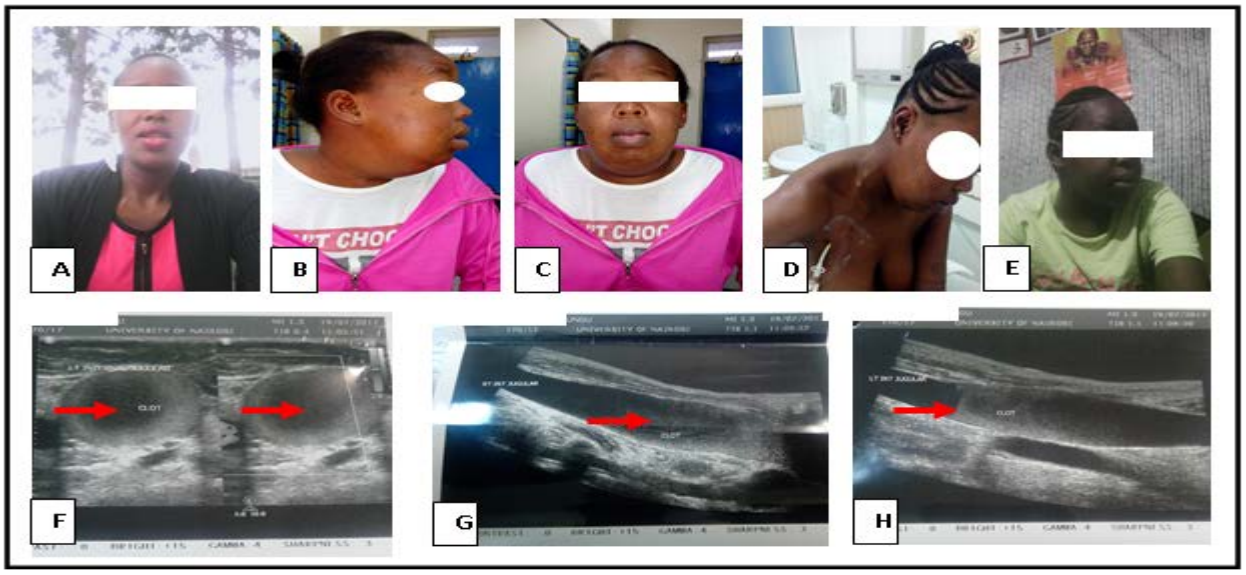

Figure 1: A - B.N face before thrombosis, **B** and **C**, B.N face at presentation, **D –**B.N face at 3 weeks before removal of the tunneled right internal jugular vein catheter, **E**- B. N face after removal of the catheter., **F-H** doppler ultrasound of the subclavian and jugular veins showing thrombi (red arrows).

B.N faired well and by the third week when the internal jugular vein catheter was being remove, she was using the arteriovenous fistula for dialysis. Her swelling neck swelling subsided significantly (Figure 1 E) and the plan was to continue using warfarin and regular INR monitoring for at least 3 months as she continued with haemodialysis.

1.2 Case number 2

M.M, 30 year-old female was diagnosed hypertension, right renal artery stenosis with resultant atrophic right

kidney and chronic parenchymal renal diasease which resulted in end-stage renal disease. Her treatment included nifedipine 20 mg twice daily and atenolol 50 mg once daily. In September 2015, furosemide 80mg once daily and carvedilol 12.5mg twice daily were added. In March 2016 tunneled catheter in the right internal jugular vein was placed, started on maintenance haemodialysis. In mid June 2016, she commenced evaluations for kidney graft transplantation. In October 2016, she suffered from suspected catheter-related infection which necessitated removal of catheter by November 2016, and temporary left subclavian catheter placed at the same time. Eight months later, in June 2017, she presented with neck lymphadenopathy, with symptoms of superior venacava vein obstruction. At that time, Doppler ultrasound scan of the neck revealed lymphadenopthy in the cervical and supraclavicular and mediastinum. No deep venous thrombosis was evidence sonographhically by then. Computed tomography (CT) scan of the chest performed in June 2017 reported normal carotid and jugular vessels with enlarged level II jugulodiagastric and supraclavicular lymphnodes bilaterally.

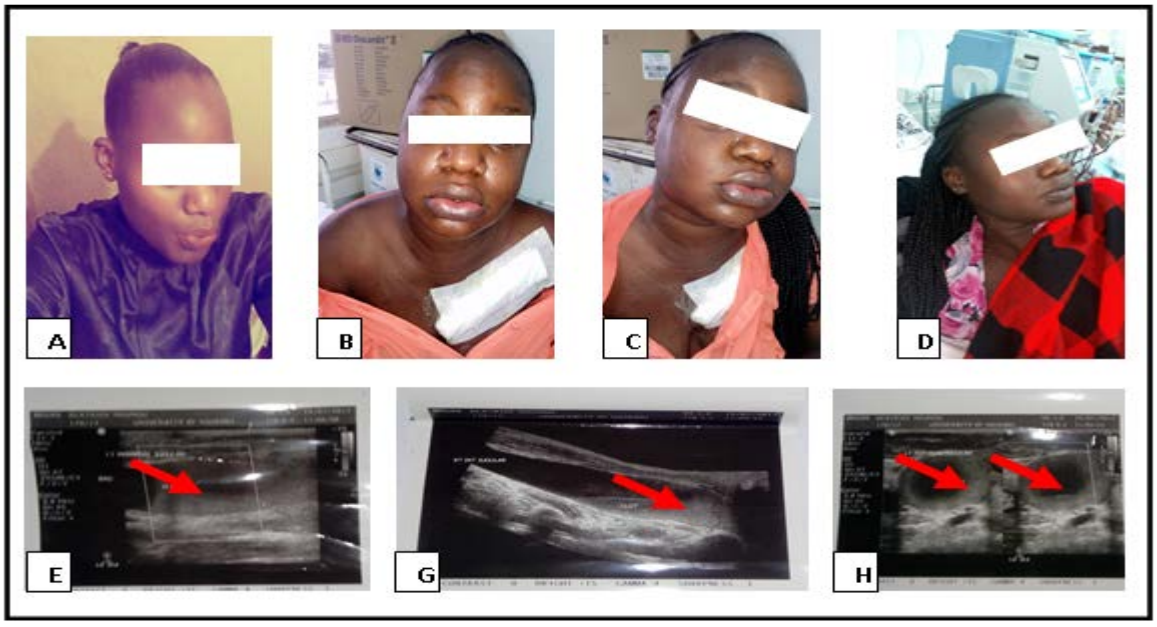

Figure 2: A- - M.M face before thrombosis, **B-C** M.M face at presentation. **D**- M.M face after 3 weeks of treatment, **E-H**: Doppler ultrasound depicting the thrombosis (red arrows)

She presented in July 2017 with worsening superior venancava syndrome. Further investigations including repeat Doppler ultrasound scan of the vessels revealed, right subclavian vein thrombus (Figure 2). She was admitted and initiated on warfarin 5mg once daily and enoxaparin 40mg subcutaneously twice daily until therapeautic INR/PTI was achieved, then continued on warfarin 5mg once daily to maintain the INR between 2-3. The left subclavian catheter was not removed, and she continued with haemodilaysis using the same vascular access. She faired well and within 5 days, she was discharged as the symptoms subsided significantly (figure 2-D). Her serial INR/PTI were 0.92/102%, at presentation 2.5/54% five days after initiation of anticoagulation, and 2.2/30.5% three weeks later. A lymph node biopsy was taken for histology for the symptoms of superior venacava obstruction could not be explained wholly by the amount of thrombosis. Preliminary histology of the node reported dermatopathic lymphadenitis as microscopic examination revealed lymphnode with expansion of interfollicular space and pigmented laden macrophage with no atypia. More consultations with pathologists are

currently underway to establish the exact cause of lymphadenopathy.

1.3 Case number 3

A.N, a 79 year-old, female, known diabetic for the last 40 years and hypertensive for last 15 years. She had been attending medical outpatient clinic from for more 30 years. She has had several admissions in the last 3 years due to diabetes complications. In March 2017, she presented with was admitted with hyperglycemia and fluid overload. She was initiated on haemodialysis via acute acute right subclavian vein catheter, which she used for one week, developed vascular access sepsis. The catheter was was removed. Her fluid status had improved and she was discharged to be reviewed after every two weeks on hydrallazine 25mg thrice daily, nifedipine 20mg twice daily, mixed insulin (30/70) 22 units in the morning and 13 units in the evening. Two weeks later, she presented in accident and emergency room with hyperglycemia and fluid overload. An acute left internal jugular catheter was inserted and was reinitiated on haemodialysis. She was admitted for 2 weeks, within when she was transitioned to a right internal jugular tunneled catheter, discharged to continue with twice weekly maintenance haemodialysis. At the end of June 2017, she presented with right upper limb, right breast and neck swelling with associated pain, which on investigations revealed thrombosis in the right internal and external jugular veins. She was admitted and treatment started. At admission, her INR/PTI was 0.96/104%, and after one week was 2.8/67%. Three weeks later the INR/PTI was 2.5/52%. She progressed well, and the superior venacava obstruction symptoms subsided significantly (Figure 3-C). She is to continue with warfarin for at least 3 months with monitoring of INR/PTI regularly as she continue with haemodialysis and management for diabetes and hypertension.

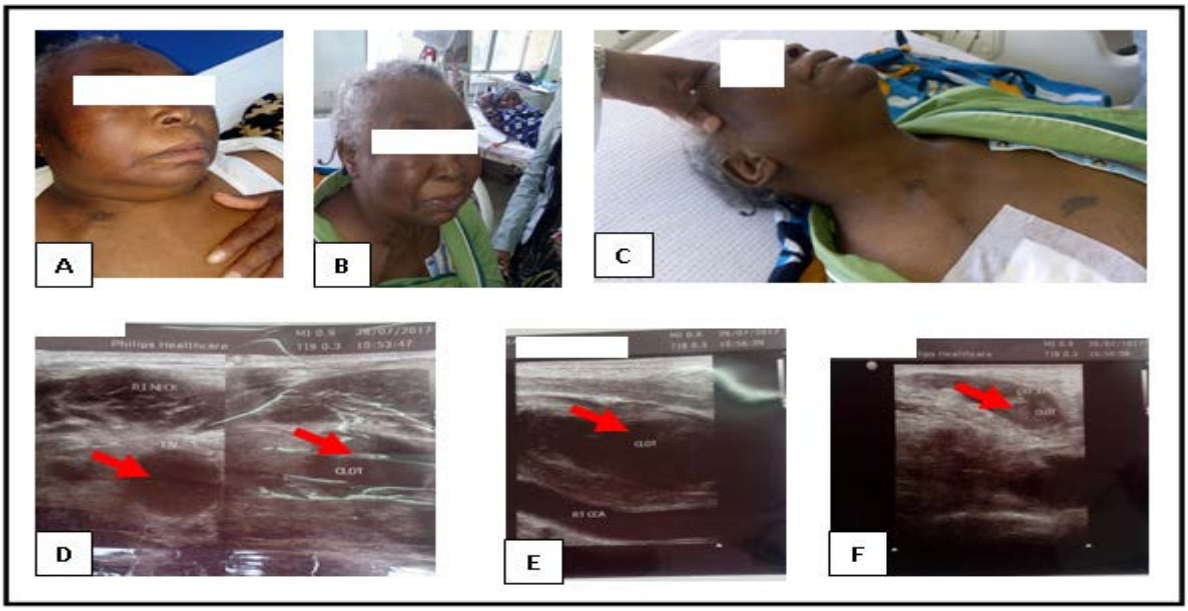

Figure 3: A- A.N face at presentation, **B-C**: -A.N three weeks after initiation of treatment. **D-F-** Doppler ultrasound depicting thrombi (red arrows).

2. Discussion and literature review

2.1 Prevalence and risk factors

Endstage renal disease patients on dialysis have elevated risks of venous thrombosis and arterial thrombosis, with history of thrombosis prior to the start of dialysis associated with an increased mortality risk [1]. The presence of a catheter inside a vein increases the risk of thrombosis, both within the catheter and in the vein [2] and these three patients had indwelling venous catheters. Tunneled catheters use for vascular access for hemodialysis is associated with a relatively high incidence of complications, with the most frequently occurring complication being dysfunction or poor flow [3], A.N and B.N had tunneled venous catheters, while M.M. had a non-cuffed, non-tunneled venous catheter. Catheter thrombosis is a common problem, frequently resulting in catheter loss with the mean patency rate ranges from 73 to 84 days [4] though in our cases we could not ascertain the cause of the malfunction A.N and B.N catheters, whether vascular thrombosis extended to the catheter lumens. The frequency with which a catheter within the central veins precipitates thrombosis of the vein is unclear, with investigators reporting varied incidences between 2-64% [5, 6]. The principal cause of access morbidity is thrombosis, representing 80-85% of complications and access failures [7-9]. Besides anatomical causes, other risk factors for access thrombosis include hypoalbuminemia, hypercoagulable states, inflammation, erythropoietin therapy, hypotension, hypovolemia, diabetes and age [3, 10].

Catheter-related thrombosis can be either extrinsic or intrinsic. An extrinsic thrombus forms outside of the catheter and is not necessarily attached to it, although the catheter or its tip may be embedded within the thrombus. An intrinsic thrombus is either forms within the catheter or completely surrounds it as a sleeve or sheath [11]. There are three types of extrinsic thrombi: Axillo-subclavian vein thrombosis where the presence of a catheter within the central veins, most commonly the subclavian, can precipitate thrombosis within the vessel. Mural thrombus where the thrombus forms on the wall of the vein or the atrium at the point of its contact with the tip of the catheter. Large intra-atrial thrombus presents as a mass within the right atrium [12]. All forms of extrinsic thrombi can, in addition to causing catheter blood flow problems during hemodialysis as were the cases with A.N and B.N, present with relatively unique clinical features that suggest the particular type of thrombus.

2.2 Presentation signs and symptoms

Neck pain and swelling are the typical presentations of internal jugular vein thrombosis [13] all these were present in our cases. Yardim and his colleagues reported a significant correlation between the number of catheter insertions and thrombosis with the frequencies of 14%, 15%, and 47% in those undergoing catheter insertion once, twice, and three times, respectively. All our three cases had had at least two venous catheters inserted. No significant relationship was found between anatomical variations and thrombosis and between C-reactive protein and thrombosis [14]. Axillo-subclavian vein thrombosis symptoms can be dramatic. Locally, the thrombus incites an inflammatory reaction with pain and tenderness at the base of the neck, the supraclavicular fossa, and the shoulder area. Obstruction of the thoracic veins may lead to edema of the arm and hand this was were evident in our cases. This is often exercise-dependent, being present only when the arm is used vigorously. In some patients, the edema is only a subjective symptom, presenting as a feeling of fullness in the fingers.

2.3 Diagnostic tests

To document the diagnosis by more objective means, digital subtraction angiography is the most sensitive and specific technique for demonstrating the presence of axillo-subclavian vein thrombosis and is considered the reference gold standard [15-19], unfortunately, this was not done in our cases. Duplex ultrasonography has emerged as the study of choice should confirmation be required. Ultrasonography was utilized in our cases given its availability, affordability and ease of operation in these patients. Overall, the diagnostic value of colour Doppler ultrasonography has sensitivity of 81-94% and specificity of 94-96% and a negative predictive value of 89% [20, 21].

2.4 Treatment/Management

The use of anticoagulation in renal failure carries an increased risk of complications, in particular bleeding, and vascular calcifications, which could annul the advantages derived from reduced thrombotic events. In our case, B.N suffered from epistaxis during the initial days after initiation of the anticoagulation. Before starting oral anticoagulant therapy it is suggested that carefully evaluation if there are potential overall benefits and to pay attention to concomitant antiplatelet therapy be undertaken [2]. None of our patients was initiated on anti-platelets therapy. Oral anticoagulants can be started within 24 hours of the initiation of heparin. Warfarin should be started at a dose of 5 mg with subsequent doses titrated to achieve an International Normalized Ratio (INR) of 2.0-3.0. If there is no contraindication to their use, thrombolytic therapy may be considered for patients with extensive thrombosis. None of our cases underwent thrombolytic therapy. In cases in which potential sites for vascular access are depleted or extremely limited, as was the case in A.N, and M.M it may be possible to preserve the catheter. However, if this strategy is chosen, the patient should be systemically anticoagulated and observed very closely [22]. All our three patients were systemically anticoagulated with regular monitoring of INR.

When symptomatic thrombosis is present, the catheter should be removed if possible. This alone may be sufficient to obtain resolution of symptoms in most cases. Anticoagulation has become the mainstay of therapy for these patients, although controlled studies have not been conducted to evaluate its effectiveness. It is recommended that the patient receive anticoagulation for a period of three months after catheter removal to prevent extension of the thrombus and to allow it to organize. Initially, severely symptomatic patients with axillo-subclavian thrombosis should be treated with a 5-7 day course of low-molecular-weight heparin. Patients with severe symptoms, significant concomitant medical illness, or a high risk for bleeding should be treated in the hospital. We considered all our three patients to have severe symptoms. For central venous catheter-induced thrombosis, the duration, site and extension of the thrombotic complication should be assessed. If thrombosis is recent and symptomatic, heparin treatment followed by oral anticoagulant therapy is suggested. For whether oral anticoagulant therapy is useful for primary prevention of thrombosis with oral anticoagulant, both within the central venous catheter and the vein where the catheter is inserted, the available evidence in favour for the use of oral anticoagulant therapy is not entirely convincing. At any rate, before such treatment is started the balance between the antithrombotic efficacy and the possible side effects should be carefully weighed. For secondary prevention of central venous catheter thrombosis if a permanent central venous catheter is in place and its

position is correct and the blood flow <250 mL/min, before replacing the central venous catheter, thrombolytic treatment followed by oral anticoagulants, aiming at an INR target between 2-3 is recommended [2]. For our cases, since none of our patients underwent thrombolytic therapy, we aimed at attainment of therapeutic INR of 2-3 before removing the catheters.

Dedicated surveillance programs have been shown to reduce major surgical interventions [23]. According to data from hospital records and the Australian and New Zealand Dialysis and Transplant Registry, implementation of a vascular access surveillance increases service utilization and is associated with a reduction in vascular access thrombosis [24]. Implementation of a vascular access surveillance increases service utilization and is associated with a reduction in vascular access thrombosis [25].

3. Conclusion

Vascular thrombosis is a common presentation in patient with endstage renal disease on haemodialysis. Catheter related vascular thrombosis is common and is associated with significant morbidity. Prompt diagnosis and initiation of treatment is important to alleviate morbidity. Clinical presentation and Duplex ultrasonography aid in diagnosis of thrombosis. Modality of treatment include thrombolytic therapy, and anticoagulation. Since thrombolytic therapy requires more experience and technical knowhow, in absence of this experience, initiation of anticoagulation is reasonable. Oral anticoagulants can be commenced within 24 hours of the initiation of unfractionated or low molecular weight heparin. Warfarin can be commenced at a dose of 5mg with a target INR of 2.0 to 3.0. The recommended duration of therapy is 3 months. Thrombolytic therapy may be considered for patients with extensive thrombosis. For patients with symptomatic thrombi, the catheter should be removed if possible. The treatment should be personalized depending on the patient condition.

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