

## Case Report

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# Venous aneurysm complicating arteriovenous fistula access and matrix metalloproteinases

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**Abstract:** Introduction: An arteriovenous fistula (AVF) for placed for hemodialysis may be burdened by one particular complication—the formation of a venous aneurysm. It has been shown that matrix metalloproteinases (MMPs) and neutrophil gelatinase-associated lipocalin (NGAL) could represent markers of disease in both venous and arterial vessels.

**Materials and methods:** This case study reports a rare case of enormous venous aneurysm-correlated MMP and NGAL levels in a woman with an AVF.

**Results:** Significantly higher levels of plasma MMP-1, MMP-8, MMP-9, and NGAL were detected in this patient during aneurysmal evaluation before the surgery; these levels significantly decreased 1, 3 and 6 months after surgery.

**Conclusion:** MMP and NGAL levels could represent a marker of aneurysmal disease, and their plasma

evaluation could help physicians to stratify the risk of complications in patients with an AVF.

**Keywords:** arteriovenous fistula, matrix metalloproteinases, MMP, neutrophil gelatinase-associated lipocalin, NGAL, hemodialysis

## 1 Introduction

Native arteriovenous fistula (AVF) is the gold standard for patients undergoing haemodialysis[1-2]; furthermore, radiocephalic and brachiocephalic access represent the sites of choice for inserting primary permanent vascular access in patients with kidney failure [3-4].

About one-third of autologous AVFs, although burdened by a lower complication rate and a better patency rate than arteriovenous grafts (AVGs), produce local complications that include thrombosis, stenosis, infection, and aneurysm formation, [5-6] with an incidence of 5–7% [7].

It has been shown that matrix metalloproteinases (MMPs) and neutrophil gelatinase-associated lipocalin (NGAL) could represent markers of disease in both venous and arterial vessels [8-22].

We report a woman with an AVF who had a rare case of an enormous venous aneurysm correlated with MMP levels.

## 2 Case Report

A 56-year-old woman was admitted to our hospital for a very large mass in her left arm. She was not a smoker and had a 15-year history of hypertension that was well controlled (115/87 mmHg) with drug treatment. In 1988 she developed chronic kidney failure secondary to a missed abortion and glomerulonephritis, requiring hemodialytic treatment; in 1990 an AVF was positioned in her left arm. Five years

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later, four AVFs had been further positioned on both upper extremities, three in the left arm and one in right. In 1999, the patient underwent a renal transplant, and dialysis was stopped. A few months later, a pulsating mass developed in the left arm of our patient without any other symptoms; therefore, neither the patient nor her doctor or her family members were concerned that it continued to grow for the next 14 years, when she finally came to our attention. At admission, a clinical examination revealed that pain and functional impairment were absent, whereas a radial pulse was present; moreover, a large expansible mass (diameter about 15 cm) was located in the antero-medial region of the left arm (Fig.1). An ultrasound scan showed a voluminous pseudo-aneurysmal mass; its significant size did not allow proper assessment of the underlying vascular access. The distal vessels were patent. Magnetic resonance angiography (MRA) showed a massive vascular-type exophytic mass with sharp margins, with an area of hypointense T1 and hyperintense T2; low flow and partially occluded venous afferences made it difficult to characterize its topography.

A blood chemical evaluation excluded the presence of infections (both reactive-C protein and leukocytes were in normal range); therefore, a venous aneurysm was diagnosed, and surgery was the treatment of choice.

Before the surgery, a blood sample was collected to evaluate the plasma MMP and NGAL levels through enzyme-linked immunosorbent assay (ELISA), consonant with our previous studies [8-22].

For surgery, an incision was made along the medial bicipital groove on the left arm (Fig. 2), and the axillary and brachial arteries upstream and downstream of the aneurysm were isolated. A very large aneurysm was found between the humeral artery and basilic vein. After aneurysmectomy (Fig. 3), the humeral artery was reconstructed. One week later, a blood sample was collected to evaluate the MMP and NGAL levels. An unpaired Student's *t* test was used for statistical evaluation; the threshold of statistical significance was set at  $*P < 0.05$ . The ELISA findings revealed significantly higher levels ( $P < 0.01$ ) of plasma MMP-1, MMP-8, MMP-9, and NGAL before the surgery; these levels decreased significantly 1, 3, and 6 months after surgery.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.



Figure 1: A very large mass in the left arm.

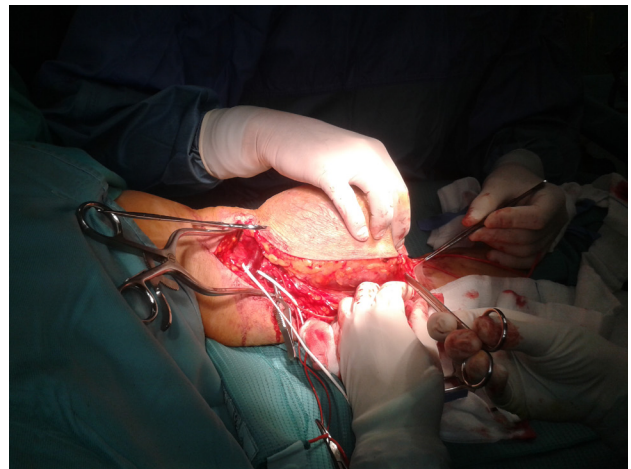
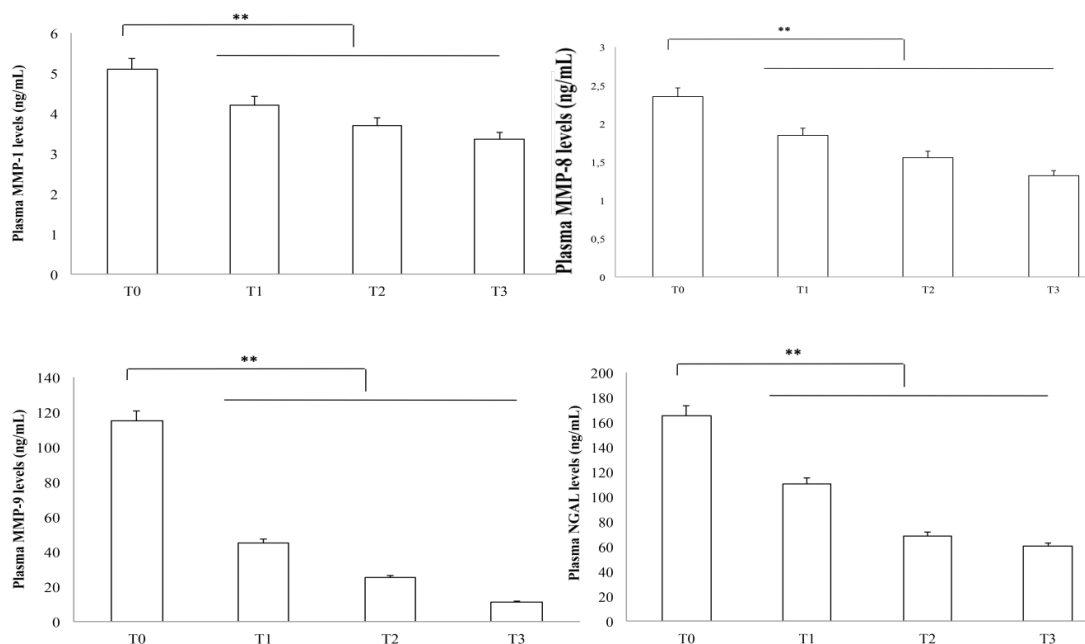


Figure 2: Incision along the medial bicipital groove on the left arm.



Figure 3: Specimen of the dissected aneurysm after aneurysmectomy.



**Figure 4:** MMP-1 (A), MMP-8 (B), MMP-9 (C), and NGAL (D) plasma levels in an aneurysmatic patient measured by ELISA. In aneurysmatic patient, levels of MMPs were measured before surgery (T0), and 1 (T1), 3 (T2), and 6 (T3) months later. \*\* $p < 0.01$  respect to T0.

### 3 Discussion

An AVF represent the first choice in patients who undergo hemodialysis because some complications, such as infection, stenosis, thrombosis, ischemia, and aneurysms, could develop [5,6,24]. Aneurysmal dilatation occurs on the arterialised vein, resulting in impairment of sites available for cannulation, thrombosis, and rupture, accompanied by massive hemorrhage, skin atrophy, ulceration, and infection; in addition, this complication significantly reduces the patient's quality of life [25].

The cause of the dilatation was degenerative mechanisms in the vein wall that resulted from repeated cannulation during dialysis, the increased blood pressure in the arterialized vein and the repeated angioplasty for the treatment of recurrent stenosis [26].

MMPs, a family of zinc-dependent enzymes that degrade the extracellular matrix play a central role in the pathophysiology of aneurysmal disease [8], as well as in several venous and arterial diseases [9-22]. As previously reported, MMP-1, MMP-3, and MMP-8 are involved in chronic diseases in which inflammation is the main pathophysiological event. In the present case, we recorded high plasmatic levels of MMP-1, MMP-8, MMP-9, and NGAL at admission that could represent the effect of chronic exposure of collagenous fibers to inflammation [9], with loss of integrity in the vascular layers. Moreover,

we documented a decrease of both MMPs and NGAL after the surgery in a time-dependent pattern, suggesting an improvement of inflammatory pathway.

In conclusion, we suggest that MMPs and NGAL could represent markers of aneurysmal disease; and an evaluation in the plasma could help physicians to estimate the risk of complications in patients with AVF.

**Conflict of interest statement:** Authors state no conflict of interest.

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