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Incidence of fibroblastic sleeve and of catheter-related venous thrombosis in peripherally inserted central catheters: A prospective study on oncological and hematological patients

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Abstract

Background: Insertion of peripherally inserted central catheters in oncological patients is potentially associated with catheter-related thrombosis and fibroblastic sleeve; the actual incidence and interactions between these two non-infective complications have never been investigated in a prospective clinical study on peripherally inserted central catheters.

Methods: In a cohort of oncological/hematological patients with peripherally inserted central catheter, we evaluated the occurrence of catheter-related thrombosis and/or fibroblastic sleeve, examining all patients by ultrasound scan at days 7, 14, 21, and 28 after insertion. We correlated our findings with the type of disease.

Results: We enrolled 254 patients with power injectable polyurethane 4Fr peripherally inserted central catheters. Ultrasound scan of the veins of the arm showed fibroblastic sleeve in 76 patients (29.9%); the fibroblastic sleeve was first detected on day 7 in 45 cases (17.7%), on day 14 in 26 cases (10.2%), on day 21 in 3 cases (1.2%), and on day 28 in 2 cases (0.79%). There was no correlation between the type of disease and the development of fibroblastic sleeve. The incidence of asymptomatic catheter-related thrombosis was 5.12%: all catheter-related thromboses were detected before day 14. There was only one case of symptomatic catheter-related thrombosis (0.39%) in a leukemia patient. Fibroblastic sleeve and catheter-related thrombosis were associated only in two cases (0.78%).

Conclusion: Fibroblastic sleeve is a frequent (29.9%) but asymptomatic finding in oncological and hematological patients with peripherally inserted central catheter, and—in the vast majority of cases—it occurs within 2 weeks after insertion. If compared to fibroblastic sleeve, asymptomatic catheter-related thrombosis is less frequent (5.51%); symptomatic catheter-related thrombosis is rare (<1%).

Keywords

Peripherally inserted central catheters, catheter-related thrombosis, fibroblastic sleeve, fibrin sleeve

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Introduction

Peripherally inserted central catheters (PICCs) are widely used for chemotherapy and supportive treatments in cancer patients and in patients with severe hematological diseases.[1,2] As any other central venous access device, PICCs are associated with some risk of intra-procedural or post-procedural complications. In this study, we have focused our attention upon two non-infective post-procedural complications, both related to the interaction between the

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catheter and the blood vessel, but quite different in terms of pathogenesis and clinical relevance: the fibroblastic sleeve (FS) and the catheter-related thrombosis (CRT). Ultrasound signs suggesting one or both phenomena are easy to detect, but differential diagnosis might be difficult.[3]

FS is a sleeve of connective tissue which develops all around the catheter as a "foreign body reaction" of the blood versus the material of the catheter. It has been erroneously named "fibrin sleeve" for years, though—according several experimental studies—it is a structured connective tissue produced by fibroblasts and macrophages, attracted by the protein fibronectin.[4] The final sleeve—when completed—contains fibroblasts, smooth muscle cells, and collagen. The pathogenesis of FS is not completely known, but it bears no relationship with the pathogenesis of CRT.[3] Also, the actual incidence of FS is not well defined, and it may vary a lot depending on the type of device and its length of stay. FS is usually asymptomatic, but it may cause catheter malfunction in rare cases, when it completely surrounds the catheter tip.

On the contrary, CRT is a repair tissue that originates from a lesion of the vein wall, and it may occur either at the site where the catheter enters the vein or where the tip of the catheter causes a mechanical trauma or chemical injury to the vein wall.[5] This repair tissue is typically attached to the vein wall, though it may enwrap the catheter as well. When the thrombotic tissue occupies the whole section of the vein, CRT is usually symptomatic. In few cases, symptomatic PICC-related thrombosis may be associated with relevant morbidity. According to a recent meta-analysis, symptomatic CRT after PICC insertion ranges between 1% and 3%, and it maybe even more frequent in patients with hematological tumors, up to 5%–7%.[6] On the contrary, the actual incidence of asymptomatic CRT in oncological patients is not known for PICCs.

In this study, we have investigated prospectively the development of FS and CRT in a cohort of oncological/hematological patients with PICCs, performing ultrasound examinations weekly for the first month after PICC insertion. Our goal was (a) to define the actual incidence (and timing of incidence) of FS and CRT, (b) to identify any possible relationship between the two phenomena, and (c) to correlate the incidence of FS and CRT with the type of neoplastic disease.

Methods

In this prospective study, we investigated all PICCs inserted by our team in a 4 month period. We enrolled exclusively adult patients (>18-year-old) with diagnosis of solid tumor or hematologic neoplastic disease. We excluded patients who had already had a previous central line of any kind (PICC, port or else) and patients who were currently receiving anticoagulant prophylaxis. In fact, in our center, the current policy is to start anticoagulant prophylaxis by low-molecular weight heparin at the moment of PICC insertion only in oncologic patients with known congenital defect of the coagulation or in oncologic patients with previous CRT.

All PICCs were power injectable polyurethane 4Fr catheters. All of them were inserted by specifically trained operators of our team, according to the PICC insertion bundle described by GAVeCeLT (the Italian Association for Long-Term Venous Access),[7] and currently adopted by our institution: preprocedural scan of the veins of both arms and of the infra/supra-clavicular area; proper hand hygiene, skin antisepsis with 2% chlorhexidine in 70% isopropyl alcohol, and maximal barrier precautions; choice of a vein of proper caliber (at least three times the external caliber of the catheter); identification of median nerve and brachial artery before venipuncture; ultrasound-guided puncture of the vein (out of plane and short axis); ultrasound-based tip navigation; tip location by intracavitary electrocardiography or by trans-thoracic echocardiography; sutureless securement; protection of the exit site with glue + transparent membrane or with chlorhexidine-releasing sponge dressing + transparent membrane.

Maintenance of the PICC was carried out according to the maintenance bundle of our institution (weekly dressing change with replacement of the sutureless device and of the transparent semipermeable membrane, after proper skin antisepsis with 2% chlorhexidine in alcohol; maintenance of patency by periodic saline flushing). For the first month, at each dressing change, we performed an ultrasound evaluation of the veins of arms and of the infra/supra-clavicular veins. FS was defined as the evidence of a layer of hypo-echoic or hyper-echoic material located all around the catheter wall, as a sort of sleeve, with a regular surface and little or no relationship with the vein wall; the sleeve was searched in any tract of the catheter visible by ultrasound.

CRT was identified by compression ultrasonography (CUS) and by direct identification of an anechoic or hypoechoic mass partially or completely occupying the lumen of the vein, with evidence of attachment to the wall. Differential diagnosis between FS and CRT is relatively easy,[8] considering that (a) FS develops around the catheter, with minimal attachment to the vein wall, while CRT is a pathophysiological phenomenon that invariably starts from the vein wall; (b) FS is never associated with local symptoms, while CRT can be either symptomatic or asymptomatic; and (c) FS may have different levels of echogenicity, while CRT—in its early stages—is always anechoic or hypoechoic; thus, a hyper-echoic image around the catheter within few weeks after insertion will probably be a sleeve rather than a CRT.

All ultrasound evaluations were performed by specifically trained nurses of our team. If the ultrasound evaluation detected abnormal findings, suggesting the presence of FS or of CRT, the patient was also examined by a physician of the Interventional Ultrasound Unit of our hospital, and

the examination completed with color Doppler techniques. All relevant information were collected in a computer-based archive, which included data about the patient (age, sex, disease, scheduled treatment, etc.), about the catheter (day of PICC insertion, vein diameter, insertion-related complications, management-related complications, etc.), and about the ultrasound evaluation (ultrasound findings).

The statistical analysis was conducted on this computer-based archive; being a purely descriptive study, no statistical comparison test was used. Since there were no reliable data from the literature suggesting the expected incidence of asymptomatic CRT and of FS in PICCs in oncological patients, we could not calculate the sample size in advance and we decided arbitrarily to limit the study to the PICCs inserted in a 4-month period. The study was designed, and the manuscript prepared, according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cohort studies.

Results

During the study period (four consecutive months), we investigated 254 PICCs in 254 patients with different oncological diseases: 204 solid tumors (Table 1) and 50 hematologic neoplastic diseases (Table 2).

Ultrasound scan of the veins of the arm showed FS in 76 patients (29.9%); the FS was first detected on day 7 in 45 cases (17.7%), on day 14 in 26 cases (10.2%), on day 21 in 3 cases (1.2%), and on day 28 in 2 cases (0.79%) (Table 3). In short, the vast majority of FS developed in the first 2 weeks after PICC insertion. All FS were asymptomatic and not associated with catheter malfunction. There was no evident correlation between the type of disease and the development of FS.

The overall incidence of CRT in the first 4 weeks after PICC insertion was 5.51% (14 patients out of 254): 13 cases of asymptomatic CRT (5.12%) and 1 case of symptomatic CRT (0.39%) (Table 4). In most cases (12 out of 14), CRT was limited to the veins of the arm. Only in two cases, CRT was localized in veins of the supra/infraclavicular area (axillary and subclavian vein). In approximately half of CRT (46%), there was a total occlusion of the lumen: though, only one patient (with leukemia) was symptomatic. The incidence of CRT was apparently lower in patients with breast cancer (1.6%) and with colonic cancer (5.9%), if compared to patients with bladder cancer (50%) and pancreatic cancer (25%) (Table 4). All CRT developed in the first 2 weeks after PICC insertion (eight within the first week and six between days 7 and 14): in the ultrasound evaluation at days 21 and 28, no additional CRT could be seen.

All CRT, either asymptomatic (n = 13) or symptomatic (n = 1), were treated by subcutaneous administration of low molecular weight heparin (100 units/kg/12 h initially and then 100 units/kg/24 h) for 3 months. There were no episodes of suspected or confirmed pulmonary embolism. In the symptomatic patient, symptoms related to venous obstruction disappeared after 48 h of treatment. All CRT patients were followed up by periodic ultrasound scan even after the end of the study period, until the CRT had healed.

Only two patients out of 254 (0.78%) developed both FS and CRT.

Table 1. Oncological patients with solid tumors.

Solid tumor	Total	Male	Female
Breast	61	0	61
Colon	34	16	18
Lung	28	24	4
Stomach	10	5	5
Pancreas	10	5	5
Rectum	8	1	7
Ovarian	8	0	8
Larynx	5	5	0
Cervix	5	0	5
Uterus	4	0	4
Bladder	4	4	0
Testicle	3	3	0
Glioblastoma	3	2	1
Prostate	3	3	0
Pharynx	3	3	0
Sigmoid	3	2	1
Bile ducts	2	1	1
Vagina	2	0	2
Facial bones	1	0	1
Liver	1	0	1
Ampulla	1	0	1
Spleen	1	0	1
Parotid gland	1	1	0
Lacrimal gland	1	1	0
Melanoma	1	1	0
Oropharynx	1	1	0
	204	78	126

Table 2. Patients with hematological disease.

Hematological disease	Total	Male	Female
myelodysplastic syndrome	2	0	2
myeloma	2	2	0
acute myeloid leukemia	1	0	1
chronic lymphocytic leukemia	4	3	1
Hodgkin lymphoma	13	5	8
non-Hodgkin lymphoma	28	14	14
	50	24	26

Discussion

PICCs are currently used in hospitalized and non-hospitalized patients for several indications, including perioperative fluid and electrolyte infusion, intravenous antibiotic therapy, parenteral nutrition, hemodynamic

Table 3. Incidence and time of detection of FS.

	Total FS	FS detected at day 7	FS detected at day 14	FS detected at day 21	FS detected at day 28
Colon	10	7	2	1	–
Breast	12	8	3	–	1
Lung	14	9	5	–	–
Non-Hodgkin lymphoma	9	6	3	–	–
Pancreas	6	3	3	–	–
Stomach	5	3	1	1	–
Chronic lymphocytic leukemia	2	2	–	–	–
Ovarian	3	1	–	1	1
Bladder	3	2	1	–	–
Larynx	2	1	1	–	–
Rectum	2	1	1	–	–
Liver	1	1	–	–	–
Glioblastoma	1	1	–		–
Uterus	1	–	1	–	–
Hodgkin lymphoma	1	–	1	–	–
Parotid gland	1	–	1	–	–
Facial bones	1	–	1	–	–
Cervix	1	–	1	–	–
Sigmoid	1	–	1	–	–
	76	45	26	3	2

FS: fibroblastic sleeve.

monitoring, and repeated daily blood sampling. They have also been widely adopted for antiblastic chemotherapy in oncological patients, either with solid tumors or with hematological disease. Although, as with any other type of venous access device, their use in neoplastic patients is associated with the potential risk of catheter-related venous thrombosis.[9]

In the past, some narrative reviews had reported the possibility of a high risk of CRT in PICCs in oncological patients and in particular in patients with hematological diseases.[10] More recent analyses have shown that the risk of symptomatic CRT is largely dependent on the technique of insertion.[2,6] An appropriate bundle for CRT prevention should include the following: (a) the choice of a vein of appropriate caliber if compared to the catheter diameter, (b) the consistent use of ultrasound guided venipuncture, (c) an accurate intraprocedural method for tip location (such as intracavitary electrocardiography or trans-thoracic echocardiography), and (d) proper securement of the PICC. The adoption of such a bundle is associated with an expected risk of symptomatic CRT of 2%–3%, somehow higher only in patients with hematological tumors (5.9%).[6] In our prospective study, adopting the GAVeCeLT bundle for safe PICC insertion,[7] which includes all the aforementioned strategies for CRT prevention, the incidence of symptomatic CRT was very low (0.39%). Interestingly, the only case of symptomatic CRT occurred in a patient with leukemia, a disease notoriously at high risk for venous thrombosis.

As regards the incidence of asymptomatic CRT in neoplastic patients with central venous access devices, the data of the literature are quite uncertain. Even more uncertain is the incidence of asymptomatic CRT in neoplastic patients with PICCs. Indeed, the actual incidence of asymptomatic CRT is unknown because of a very important bias: it is possible that in many studies the presence of FS might have been mistakenly interpreted as asymptomatic CRT. As far as we know, our study is the first prospective study investigating simultaneously the incidence of CRT and FS in a population of oncological patients with PICC, adopting clear criteria for differentiating these two phenomena.

The results of our study suggest that both FS and asymptomatic CRT are complications that mostly occur in the first 2 weeks after PICC insertion. Confirming previous reports,[3] our study found that the incidence of FS is higher (approximately 30%) if compared to the incidence of asymptomatic CRT (approximately 5%). It is possible that previous studies ignoring the differences between FS and CRT may have overestimated the actual incidence of asymptomatic CRT.

In our cohort of oncologic patients with PICCs, both phenomena—asymptomatic CRT and FS—were quite harmless. All FS were asymptomatic and not associated with any catheter malfunction. We decided to treat asymptomatic CRT, though this is an unsolved issue in the literature: there is no hard evidence that asymptomatic CRT localized to the veins of the arm should be treated.[5]

Table 4. Incidence of CRT and time of diagnosis.

	Total CRT (%)	CRT detected at day 7	CRT detected at day 14
Lung (n = 28)	4 (14.3%)	3	1
Bladder (n = 4)	2 (50%)	1	1
Colon (n = 34)	2 (5.9%)	1	1
Pancreas (n = 10)	2 (20%)	1	1
Stomach (n = 10)	2 (20%)	1	1
Breast (n = 61)	1 (1.6%)	1	–
Chronic lymphocytic leukemia (n = 4)	1 (25%)	1[a]	–
	14	9	5

CRT: catheter-related thrombosis.
[a]The only symptomatic case of CRT.

However, all cases of CRT (including the only symptomatic one) had a very rapid and favorable outcome, with no apparent relevant morbidity. From our experience, it is impossible to infer how many asymptomatic CRT might have become symptomatic, if not treated.

The possible relationship between the development of FS and the occurrence of CRT has been sometimes discussed in the literature.[3] Our clinical data suggest that these two catheter-related phenomena are not related: only two patients out of 254 developed both FS and CRT.

There is some discussion in the literature also about the hypothetical relationship between FS and catheter-related infection,[11] as well as between CRT and infection. In our study, we had no catheter related infections in the first 4 weeks of follow-up, though almost 30% of patients had developed a FS evident at ultrasound. Therefore, it seems unlikely that FS may act as a predisposing factor for bacterial colonization and catheter-related infection.

As regards the potential relationship between type of disease and development of FS and/or CRT, since there was a wide dispersion of different diagnoses in our patient population, we cannot draw significant conclusions. The overall impression is that FS developed independently from the type of neoplastic disease: in particular, there was no significant difference between solid tumors and hematologic diseases: the incidence of FS was 31.4% in solid tumors versus 24% in hematological patients. As regards the asymptomatic CRT, some types of solid tumors (breast and colon) were apparently less prone to thrombosis if compared to other solid tumors (pancreas and bladder), though the numerosity of the sample was not appropriate for bearing a statistically significant difference.

Our study has two main limitations. First, though we report a high number of cases, this is still a monocentric study, so that our data cannot be automatically transferred to other centers that may use different protocols of PICC insertion and of PICC management. Second, we have limited our follow-up to 4 weeks; though there is some evidence in the literature that most CRT and most FS develop in the first month after PICC insertion, it is nonetheless possible that some of these phenomena may occur even later in the natural history of the device.

Conclusion

Our study suggests that it may be clinically important to differentiate between FS (a harmless pathophysiological phenomenon frequently associated with PICC insertion) and catheter-related venous thrombosis (less frequent, but potentially associated with some morbidity). The inability of discriminating between FS and CRT may lead to an unnecessary anticoagulant treatment in a high percentage of patients with PICCs (even 30%), with a relevant waste of resources and the added possibility of some undesired side effects secondary to the treatment itself. Also, our study confirms that the risk of symptomatic CRT after PICC insertion is very low, even in neoplastic patients, either with solid tumors or hematological disease, when a proper insertion bundle is adopted.

Authors' note

All authors fulfill the conditions for authorship.

Declaration of conflicting interests

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Ethical approval

The study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Ethical committee of our Hospital.

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