Digital ischaemia aetiologies and mid-term follow-up
A cohort study of 323 patients

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Abstract
Upper extremity digital ischaemia (UEDI) is a rare heterogeneous condition whose frequency is 40 times less than that of toe ischaemia. Using a large cohort, the aim of this study was to evaluate aetiologies, prognosis and mid-term clinical outcomes of UEDI. All patients with UEDI with or without cutaneous necrosis in a university hospital setting between January 2000 to December 2016 were included. Aetiologies, recurrence of UEDI, digital amputation and survival were analyzed retrospectively.

Three hundred twenty three patients were included. UEDI due to cardio-embolic disease (DICE) was the highest occurring aetiology with 59 patients (18.3%), followed by DI due to Systemic Sclerosis (SSc) (16.1%), idiopathic causes (11.7%), Thromboangiitis obliterans (TAO) (9.3%), iatrogenic causes (9.3%), and cancer (6.2%). DICE patients tended to be older and featured more cases with arterial hypertension whereas TAO patients smoked more tobacco and cannabis. During follow-up, recurrences were significantly more frequent in SSc than in all other tested groups (P < .0001 vs idiopathic and DICE, P = .003 vs TAO) and among TAO patients when compared to DICE patients (P = .005). The cumulated rate of digital amputation was higher in the SSc group (n = 18) (P = .02) and the TAO group (n = 7) (P = .03) than in DICE (n = 2).

This retrospective study suggests that main aetiologies of UEDI are DICE, SSc and idiopathic. This study highlights higher frequency of iatrogenic UEDI than previous studies. UEDI associated with SSc has a poor local prognosis (amputations and recurrences) and DICE a poor survival. UEDI with SSc and TAO are frequently recurrent.

Abbreviations: DICE = digital ischaemia due to cardio-embolic disease, SSc = systemic sclerosis, TAO = thromboangiits obliterans, UEDI = upper extremity digital ischaemia.

Keywords: upper extremity digital ischaemia, systemic sclerosis, thromboangiitis obliterans

1. Introduction
Upper extremity digital ischaemia (UEDI) is a peripheral arterial disease. Diagnosis remains a real challenge and consequently evaluation of aetiologies and determination of therapeutic strategies has proved difficult.11–5 The incidence of UEDI is about 2 cases per 100,000 persons per year.16,7 The frequency of symptomatic UEDI is forty times less than the frequency of lower limb ischaemia.

The main causes identified in literature are cardiac or arterial embolism, local thrombosis, systemic autoimmune connective tissue diseases (especially systemic sclerosis), vasculitis or traumatic injury.8

In literature, only a few studies have focused on the prevalence of UEDI’s aetiologies. Only 2 retrospective studies about, with a cohort of over 100 patients, were reported.7,9 Moreover, in patients diagnosed with UEDI, midterm outcomes were rarely described. There are few studies about the midterm follow-up of UEDI. Three of them concerned the follow-up of patients with a specific aetiology: cancer-induced UEDI,9 hypothenar hammer syndrome,10 systemic sclerosis.11 Only 3 studies were about general follow-up of UEDI, both with a limited number of cases.12–14

This study evaluated aetiologies in a large cohort and assessed midterm clinical outcomes of patients diagnosed with UEDI.
2. Material and methods

This retrospective cohort study included patients hospitalized for UEDI and outpatients visiting for UEDI in a university hospital between January 1, 2000, and December 31, 2016. We identified patients, based on ICD-10 through the medical data processing department. This study was approved by the Local Ethics Review committee. UEDI inclusion criterion was the first episode of UEDI diagnosed, defined by painful and digital blanching, cyanosis, ulceration of the fingers, gangrene or change of cutaneous temperature, due to vascular pathology and excluding isolated Raynaud’s phenomenon. Difference between Raynaud’s phenomenon and UEDI was made by performing laser Doppler imaging or acral plethysmography.

All cases of UEDI included ischaemic involvement of the fingers, but we also included cases of UEDI involving hand.

Clinical assessment included demographic data (age, gender, occupation), medical history, cardiovascular risk factors, substance abuse, number of recurrence, midterm clinical outcomes and cardiovascular events (stroke, myocardial ischaemia, lower limbs ischaemia).

For each case, we collected the following diagnostic tests: complete blood count, anti-nuclear antibodies, cryoglobulinemia, CRP, fibrinogen, electrophoresis of blood proteins, ECG and holter-ECG on 24 hours, capillaroscopy, transthoracic echocardiography, echography Doppler, laser Doppler imaging or acral plethysmography.

Each aetiology was determined as follows: Systemic Sclerosis cases (SSc) were diagnosed through ACR/EULAR 2013’s criteria.[15] Thromboangiitis obliterans cases (TAO) by Mills 2003’s criteria.[16] Cardio-embolic (CE) diseases were diagnosed through ultrasound criteria and Holter monitoring. Vasculitis cases were diagnosed with histology or by cryoglobulinemia positivity or ANCA positivity and further with giant cell arthritis and Takayasu’s Arteritis by ACR or Ishikawa’s criteria. Thrombophilia was determined through specific biological tests. Cancers were diagnosed on histologic evaluations for solid tumors and haematologic malignancy by histology and specific lab tests as molecular biology.

The iatrogenic aetiology was defined as follows: for drug-induced iatrogenic ischaemia by intrinsic and extrinsic probability and for technical-induced iatrogenic ischaemia (such as artery cannulation), by corresponding temporality. The hypotenar hammer syndrome was identified with the help of occupational health service. When criteria were not found, diagnosis was made following intrinsic and extrinsic causality. Idiopathic ischaemia was defined as such after negative clinical, laboratory and imaging examination. When several aetiologies could be incriminated, we chose to include the UEDI case in the aetiology most susceptible to be responsible for.

Recurrence was defined with the same inclusion and exclusion criteria than the first episode of UEDI. In absence of symptoms resolution, recurrence were only identified if occurring in another finger.

Midterm follow-up was performed by chronological analysis of medical records and by regimenting telephone interviews with patient’s general practitioner.

2.1. Statistical analysis

Results of the sixth most occurring aetiology were expressed as mean ± standard deviation (SD) or as median, range. Categorical variable for the 6 groups were compared using Chi-Squared tests or Fisher exact tests when any of the expected cell counts of a 2 x 2 table was less than 5. Comparisons of quantitative variables were performed using Student t test. ANOVA test was performed with a Bonferroni correction after tests to individualize group differences. A P value <.05 was considered statistically significant. Survival curves were developed to compare cardio-embolic, SSc, idiopathic and TAO groups. Only new events were considered. Overall survival rates, survival free of digital ischaemia, survival free of cardiovascular events (stroke, acute myocardial infarction or acute lower limb ischaemia) and survival free of finger amputation were estimated using the Kaplan–Meier method and comparisons between groups were assessed using the log-rank test. All calculations were done using Graph Pad Prism 6.

3. Results

This study included 323 patients. Three hundred eight patients were considered to be acute UEDI and 15 patients were considered to be chronic UEDI. The aetiologies of UEDI are presented in Table 1.

The mean follow-up was 56.7 months. Iatrogenic patients were divided up as follows: 33% of cases (10 patients) had vascular steal syndrome from arteriovenous fistula creation (AVF) and 22.2% (6 patients) presented UEDI after vasoconstrictive drug use, as norepinephrine, in critical care department. Other iatrogenic UEDI (15 patients) were 5 cases after radial artery puncture, 3 cases of radiation-induced stenosis, 1 case of other adverse effects of AVF creation (arterial thrombosis), 2 cases of other drug-induced side effect (mesalazine and tocilizumab), 1 case of arterial thrombosis after a local corticosteroid injection of carpal tunnel syndrome therapy, 1 case of thrombosis of a carotid-carotid bypass and subclavian artery bypass in a patient with an atheromatous thoracic aorta aneurysm and 1 case of graft versus host reaction with a systemic sclerosis-like presentation.

UEDI was associated with cancer in 6.2% of cases. Median time between diagnosis of UEDI and diagnosis of cancer was 14.3 months. Haematologic malignancies (45% of all neoplasia) were represented as follows: 30% of myeloproliferative neoplasms (3 Polycythemia Vera, 1 essential thrombocythemia, 1 secondary...
myelofibrosis after essential thrombocythemia, 1 myeloid leukemia), 2 cases of multiple myeloma and 1 case of acute leukemia. Solid tumors (55% of all neoplasia) were distributed as follows: 35% of adenocarcinomas (2 colonic adenocarcinomas, 1 esophageal adenocarcinoma, 1 cholangiocarcinoma, 2 metastatic pulmonary adenocarcinomas, 1 ovarian adenocarcinoma), 2 cases of hepatic neoplasia; 1 case of Squamous cell carcinoma and 1 thymoma. The main mechanism of UEDI in this group was cancer-induced thrombophlebitis (n=19), and 1 case of embolism.

Connective Tissue Disease (CTD), without systemic sclerosis, accounted for 3.1% of cases of digital ischaemia with 5 cases of mixed connective tissue disease and 1 anti-synthetase syndrome. Among the 11 cases of UEDI due to atherosclerosis, we found 10 cases of atherosclerosis stenosis without subclavian aneurysm and 1 case of the aortic arch aneurysm.

UEDI was associated with vasculitis in 6.2% of cases: 3 Giant cell arteritis, 2 Takayasu’s arteritis, 2 cryoglobulinemia, 1 necrotizing small vessel vasculitis and 2 unclassifiable vasculitis.

In the thrombophilia group, antiphospholipid syndrome was associated with UEDI in 6 cases, and antithrombin deficiency in 1 case.

Infectious diseases were 4 cases of purpura fulminans and 3 cases of endocarditis.

The 5 cases of vasospasm were 3 cases of narcotic intra-arterial injections (cocaine, heroin) and 2 patients who misused buprenorphine, 1 with a cold exposure during work time and 1 extreme vasospasm on peripheral vascular disease. Peripheral embolisms showed 2 subclavian artery thrombosis and 1 aortic arch partial thrombus.

Lastly, 18 cases were considered as “Other” defined by: 4 cases of calciphylaxis, 1 frost injury, 1 circulatory failure, 1 prernecrotizing state of severe acrocyanosis, 1 abscess on a needle stuck in muscle in a former drug addict, 1 disseminated intravascular coagulation, 2 cases of cold agglutinin disease and 2 cases of severe carpal tunnel syndrome. There were also 3 arteriovenous malformations and 2 congenital stenosis (1 brachial artery stenosis, 1 brachiocephalic trunk stenosis).

Trumatic causes (n=9) were mostly due to violent direct traumas: car accident, stab wounds, attempted suicide, and work accidents.

For 8 patients at least 2 aetologies could have been incriminated, we chose to include this UEDI case in the aetiology most susceptible to be responsible for: 5 cases were considered as “Other,” 2 cases were included in infectious diseases group, 1 case was included in traumatic group. The main characteristics of the population, as well as characteristics of the 5 most represented aetiologies of UEDI are presented in Table 2.

Digital ischaemia due to cardio-embolic disease (DICE) patients were significantly older than SSc, idiopathic and iatrogenic groups (P<.001); they presented significantly more hypertension than SSc and TAO groups (P<.0001) and also comprised less tobacco smokers than in the idiopathic group (P<.0001). In the SSc group, there were significantly more women than in the TAO group (P=.0006), the idiopathic group (P=.03) and the iatrogenic group (P=.04). TAO patients were significantly younger than those in the iatrogenic group (P<.0001) and in the neoplasia group (P<.01). There were also significantly more tobacco smokers than in all other groups (P<.0001) and more cannabis smokers than in DICE (P<.0002), neoplasia (P=.03), SSc and iatrogenic groups (P=.01). In the TAO group, there were significantly more men than in the DICE (P=.048) and neoplasia (P=.04) groups and patients were also significantly less hypertensive than in DICE (P<.0001), neoplasia (P=.01), iatrogenic and idiopathic groups (P=.003).

Medical treatment was different depending on the aetiology of UEDI (Table 3). DICE were significantly more treated with anticoagulant therapy than in all other groups (P<.0001 for idiopathic, iatrogenic, SSc and TAO groups, P=.007 for neoplasia group). Whereas, in the TAO group antiplatelet drug was significantly more used than in all other groups except idiopathic (P=.01 for SSc and neoplasia groups, P<.0001 for DICE and iatrogenic groups). In the TAO group, we also found more calcium channel blocker therapy than in DICE (P<.0001), the neoplasia group (P=.003) and the iatrogenic group (P=.0004). Almost all the prescriptions of Bosentan were in the SSc group and 1 case in mixed connective tissue disease. The

### Table 2

| General characteristics of 4 most commonly occurring aetiologies. | All aetiology n = 323 | CE n = 59 | SSc n = 52 | Idiop n = 38 | TAO n = 30 | Latro n = 30 | P value |
|---------------------------------------------------------------|----------------------|--------|----------|-------------|-----------|-----------|--------|
| **Mean age in years (±SD)**                                  | 60.5 ± 18.1          | 81.7 ± 15.2 | 53.4 ± 16.7 | 60.2 ± 21.7 | 43.5 ± 9.9 | 59.0 ± 19.0 | <.0001 |
| **Female n, (%)**                                            | 183 (56.7%)          | 35 (59.3%) | 39 (75.0%) | 19 (60.0%) | 11 (36.7%) | 17 (54.8%) | .02    |
| **CVRF**                                                     |                      |         |          |             |           |           |        |
| Diabetes n, (%)                                              | 32 (9.9%)            | 7 (11.9%) | 2 (3.8%) | 6 (15.8%) | 1 (3.3%) | 6 (19.4%) | .11    |
| Hypertension n, (%)                                          | 141 (43.7%)          | 42 (71.2%) | 14 (26.9%) | 20 (52.6%) | 5 (16.7%) | 17 (54.8%) | <.0001 |
| Tobacco smokers n, (%)                                       | 117 (36.2%)          | 5 (8.5%) | 13 (25.0%) | 17 (44.7%) | 30 (100%) | 8 (25.8%) | <.0001 |
| Dyslipidemia n, (%)                                          | 73 (22.6%)           | 19 (32.2%) | 10 (19.2%) | 11 (28.9%) | 4 (13.3%) | 6 (19.4%) | .28    |
| CV Heredity n, (%)                                           | 22 (6.8%)            | 6 (10.7%) | 1 (1.9%) | 2 (5.3%) | 3 (10.0%) | 1 (3.2%) | .14    |
| Obesity IIMC > 30 kg/m² n, (%)                               | 17 (5.3%)            | 6 (10.7%) | 1 (1.9%) | 3 (7.9%) | 1 (3.3%) | 5 (16.1%) | .36    |
| Substance abuse n, (%)                                       | 14 (4.3%)            | 0 (0.0%) | 1 (1.9%) | 4 (10.5%) | 3 (10.0%) | 1 (3.2%) | .05    |
| Alcohol n, (%)                                               | 40 (12.4%)           | 3 (5.1%) | 7 (13.5%) | 5 (13.2%) | 8 (26.7%) | 4 (12.9%) | .07    |
| Cannabis smokers n, (%)                                      | 17 (5.3%)            | 1 (1.7%) | 2 (3.8%) | 3 (7.9%) | 7 (23.3%) | 0 (0.0%) Measurement | .0004 |
| **Laboratory Measurement**                                   |                      |         |          |             |           |           |        |
| Hemoglobin (g/dL)                                            | 12.7 ± 2.1           | 13 ± 1.5 | 13.1 ± 1.7 | 12.9 ± 1.7 | 13.6 ± 1.7 | 11.5 ± 1.9 | .4     |
| Platelets (G/L)                                              | 267 ± 132.9          | 236 ± 84.8 | 277.9 ± 160.9 | 305 ± 155.2 | 300.6 ± 65.2 | 218 ± 132.2 | .05    |
| CRP (mg/L)                                                   | 22.4 ± 44.1          | 19.5 ± 25.3 | 12.0 ± 22.9 | 28.4 ± 36.9 | 8.3 ± 6.5 | 74.4 ± 138.4 | .02    |
| Fibrinogen (g/L)                                             | 6 ± 14.6             | 4.4 ± 1.4 | 3.5 ± 0.7 | 3.9 ± 1.2 | 4.1 ± 0.9 | 4.8 ± 2.5 | .08    |

CVRF = cardiovascular risk factors, CE = cardio-embolic, latro = iatrogenic, Idiop = idiopathic, SSc = systemic sclerosis, TAO = thromboangitis obliterans
Idiopathic group receive significantly more anticoagulant therapy than SSC ($P < .0001$) and TAO groups ($P = .003$).

Surgical revascularization was performed by Fogarty catheter or bypass when the patient had sensitive or motor neurological deficit. 64.4% of DICE group benefit of surgical revascularization, 25.8% of iatrogenic group and 18.4% of idiopathic group.

In DICE group successful surgical revascularization were significantly more often than all other groups ($P < .0001$). Idiopathic group also had significantly more surgical revascularization than the SSc group ($P = .002$) and the TAO group ($P = .02$).

In DICE group, 35.6% were disqualified for surgical procedures because of lack of anatomical feasibility for revascularization.

When surgical revascularization was not possible, patients benefit of medical treatment and supervision.

The recurrence rate was variable and dependent on aetiology (Fig. 1A). Recurrence of UEDI was significantly greater in the SSc group ($n = 37$) than in all other groups ($P < .0001$ vs idiopathic and DICE, $P = .0004$ vs iatrogenic $P = .003$ vs TAO and $P = .007$ vs neoplasia). In the TAO group, recurrence was significantly greater ($n = 6$) than in DICE ($n = 1$) ($P = .005$). There were only 3 recurrences in the idiopathic group.

The frequency of digital amputations varied according to aetiologies (Fig. 1B). The cumulated rate of digital amputation was higher in the SSc group ($n = 18$) ($P = .02$) and the TAO group ($n = 7$) ($P = .03$) than in DICE ($n = 2$). In terms of survival free of amputation, there were no significant differences between the other groups. There were only 4 amputations in the idiopathic group.

Cardio-vascular (CV) events also varied (Fig. 1C): the DICE group had more CV events ($n = 17$) than idiopathic UEDI ($n = 8$) ($P = .04$), SSc ($n = 7$) ($P = .0005$) and the TAO group ($n = 4$) ($P = .03$).

The overall survival was different depending on aetiology (Fig. 1D). Mortality was more frequent in DICE ($n = 27$) than the SSc ($n = 14$) ($P < .0001$), idiopathic ($n = 10$) ($P = .0093$) and TAO ($n = 5$) ($P = .0007$) groups. However, there was no difference between the idiopathic group and SSc ($P = .12$), iatrogenic ($P = .51$) and TAO groups ($P = .29$).

### Table 3

|                | CE n = 59 | SSC n = 52 | Idiop n = 38 | TAO n = 30 | Iatro n = 30 |
|----------------|-----------|------------|--------------|------------|--------------|
| Iloprost n, (%)| 4 (6.8%)  | 14 (26.9%) | 9 (23.7%)    | 13 (43.3%) | 3 (9.7%)     |
| Oxygenation n, (%)| 8 (1.6%) | 9 (17.3%)  | 9 (23.7%)    | 7 (23.3%)  | 3 (9.7%)     |
| Warming n, (%) | 13 (22.0%)| 33 (65.5%) | 18 (47.4%)   | 20 (66.7%) | 4 (12.9%)    |
| Calcium channel blocker n, (%) | 1 (1.7%) | 20 (38.5%) | 15 (39.5%)   | 18 (60.0%) | 4 (12.9%)    |
| Antplatelet therapy n, (%) | 5 (8.5%) | 26 (50.0%) | 24 (63.2%)   | 24 (80.0%) | 8 (25.8%)    |
| Anticoagulant n, (%) | 54 (91.5%)| 3 (5.8%)   | 20 (52.6%)   | 5 (16.7%)  | 12 (38.7%)   |
| Bosentan n, (%) | 0 (0.0%)  | 5 (9.6%)   | 0 (0.0%)     | 0 (0.0%)   | 0 (0.0%)     |

CE = cardio-embolic, SSC = systemic sclerosis, Iatro = iatrogenic, Idiop = idiopathic, TAO = thromboangiitis obliterans

Figure 1. Long-term follow-up and survival idiopathic (n = 30), Systemic sclerosis (n = 52), TAO (n = 38), Cardio-embolic (n = 59), iatrogenic (n = 30) (A). Survival free of recurrence of UEDI curves; (B). Survival free of digital amputations; (C). Survival free of cardiovascular events; (D). Overall survival. UEDI = upper extremity digital ischaemia, TAO = thromboangiitis obliterans.
4. Discussion

This study on upper extremity digital ischaemia is a large cohort with 323 patients encountered in tertiary center recruitment in vascular pathology and shows diversity of aetiology and clinical evolution.

DICE recurs only in a small number of cases in this study. Conversely, patients with SSC and TAO presented a higher number of recurrences. Similarly, patients with SSC/TAO-associated UEDI had a higher number of cases requiring amputation than DICE. This chronic ischaemia may be due to the chronicity of vascular lesions and the disappearance of microcirculatory flow reserve, associated with distal involvement. In contrast, DICE occurs in the arteries of a larger caliber, usually without pre-existing distal lesions, which explains the success of surgical management and the low amputation rate. DICE, however, is likely to be a marker of overall cardiovascular risk as patients with DICE have more cardiovascular events and have higher mortality than other UEDI groups.

This study showed proximity between DICE and idiopathic UEDI groups. Indeed, there are no survival differences without recurrence of UEDI and no difference in amputation rates between DICE and the idiopathic UEDI group. However, the DICE group had higher mortality and cardiovascular events while the idiopathic UEDI tended to showcase more cardiovascular events than other groups of UEDI. This might suggest that idiopathic UEDI may well be unidentified DICE although in this study, we did not find a significant difference. The low rate of recidivism is also in favor of this proximity.

In this study, aetiologies of the digital ischaemia are numerous and, compared to previous studies, there are differences in the distribution of aetiologies. Table 4 presents the largest studies on digital ischaemia ever reported in literature.

In this study, CE disease is the highest-occurring aetiology of UEDI accounting for 18.3% of cases, while in literature; this aetiology distribution rate was low for all studies except for the study of Skeik et al. Indeed, Skeik et al study also found CE disease to be the highest-occurring aetiology of UEDI with 46.9% of cases.[14] Previous studies have also shown connective tissue diseases to be the highest occurring aetiology of UEDI, [7,9,13,17–20] In this study, however, all CTD accounted for 19.2% of UEDI while systemic sclerosis accounted for 16% of cases. Indeed, most of the data are derived from studies of digital ischaemia, concerning a specific aetiology or a range of clinical outcomes from internal medicine departments, where connective tissue disorders are very strongly represented. Moreover, our inclusion criteria also included hand ischaemia rather than only limited finger ischaemia, as typically employed, which may have contributed to a greater recruitment of CE patients. Same conclusion can be apply to Skeik et al study whom included patient with extended ischemia of the upper extremity.[14] Our findings showed that UEDI of undetermined origin, after well-conducted explorations, is not uncommon and accounts for 11.7% in our study. In the literature, idiopathic digital ischaemia accounts for 1.6% to 22% of cases.

The iatrogenic cause was the fourth highest-occurring aetiology, in this study, with a rate of 9.6% vs 0 to 6.3% in literature.[7,9,13,14,17–20] It is interesting to notice that for 3 of the 8 previous studies, iatrogenic aetiology was not at all sought. This strong representation is linked to a broad recruitment of patients, in critical care units, with more drug-induced iatrogenic UEDI. Additionally, the results of previous studies may be limited by the era in which research was carried out as intra-arterial proceedings have developed significantly, particularly in recent years. However, several case-reported has been published on the iatrogenic cause of UEDI.[21–24]

Cancer-associated UEDI was found in 2% to 15% of cases in the previous studies. In this study, as in Le Besnerais et al,[9] the most common histologic type was adenocarcinoma. The myeloproliferative diseases were also frequent here, accounting for 30% of digital ischaemia associated with cancer. The time between UEDI and cancer diagnosis varied, between 2 months in a study with intensive initial investigation[19] and 14.3 months in this study, after a clinical examination, standard blood test and clinical follow-up.

As for treatment, our study was consistent with other studies in literature.[25–29] Iloprost is frequently used in UEDI due to SSC and Bosentan has proven efficiency to prevent recurrence of UEDI due to SSC.[25–27] In our study, we did not include treatment with phosphodiesterase inhibitors as it was still in the test during this period.

As for surgical revascularization, previous studies show that revascularization either using bypass or arterialization were both efficient to improve UEDI when occurring in arteries of a large caliber as for DICE.[28,29] The surgical studies both recommend anticoagulant therapy after surgery which is consistent with our study where anticoagulant therapy was more often used in DICE.[28–30]

This study has several limits; patients were included retrospectively during a significant period of 16 years and so there has been data loss. For idiopathic cases, we managed to find bloods tests results in 92.5% of the cases and morphological tests results in 86.6%. For a total of 5 cases without blood tests found and 9 cases without morphological tests found.

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**Table 4**

Comparison of aetiologies in other studies.

| All CTD | CE | SSC | Idiop | Iatro | TAO | Cancer | Atheroma | Vasculitis | HHS |
|---------|----|-----|-------|-------|-----|--------|----------|------------|-----|
| Present study n=323 | 19.2% | 18.3% | 16.0% | 11.7% | 9.3% | 9.3% | 6.2% | 3.4% | 3.1% | 1.6% |
| Carpentier and al 2005[7,17] n=278 | 33.0% | 8.6% | 26.0% | 4.0% | 0.3% | 10.0% | 4.0% | 15.0% | 0.0% | 15.0% |
| Le Besnerais and al 2014 [9] n=100 | 10.0% | 8.0% | 10.0% | 10.0% | NA | 22.0% | 15.0% | 4.0% | 0.0% | 13.0% |
| Cailleux and al 1999 [19] n=96 | 26.0% | 6.2% | 26.0% | 10.5% | NA | 11.5% | 5.0% | NA | NA | NA |
| Vaysrair and al 1977 [19] n=86 | 48.8% | NA | 39.0% | 19.0% | NA | 4.6% | 3.4% | 8.0% | 8.1% | 2.3% |
| Skeik and al 2015 [14] n=64 | 0% | 46.9% | 0% | 1.6% | 6.3% | 4.7% | 4.7% | 17.2% | 1.6% | 7.8% |
| Cailleux and al 1994 [20] n=45 | 27.0% | 9.0% | 0.0% | 4.0% | 0.0% | 13.0% | 2.0% | 16.0% | 0.0% | 11.0% |
| Koe and al 2011 [13] n=36 | 42.0% | 6.7% | 14.0% | 22.0% | 2.8% | 0.0% | 0.0% | 11.0% | 0.0% | 33.0% |
| Abdallah and al 2009 [21] n=25 | 36.0% | 4.0% | 12.0% | 4.0% | 0.0% | 20.0% | 8.0% | 20.0% | 12.0% | 0.0% |

CTD = connective tissue disease, CE = cardio-embolic; HHS = hypothermic hammer syndrome, Idiop = idiopathic, Iatro = iatrogenic, NA = not available, Neo = neoplasia, SSC = systemic sclerosis, TAO = thromboangiitis obliterans.
We presented episodes of UEDI from tertiary center recruitment in vascular pathology, where prevalence of CTD and multiple comorbidities are higher. That can explain over representation of CTD and DICE in our study. Because diagnosis of occupational pathologies is carried out upstream of our center, they are under-represented in our study while they represent up to 33% in some UEDI studies.

The etiological explorations of UEDI are often very limited and very variable depending on the specialty in charge of the patient. A minimal investigation could be proposed in order to identify most of the causes of UEDI.

All clinical interrogation could contain: full list of drugs with and without medical prescriptions taken by the patient, drug-abuse, past episode of UEDI, the notion of palpitations or an irregular pulse at the time of the episode of UEDI.

Medical assessment could contain: Allen test, ECG and holter-ECG, capillaroscopy, transthoracic echocardiography and if previous tests are negative a transesophageal echocardiography could be discuss.

Biological tests could contain complete blood count, CRP and, if cardiological investigations are negative or in case clinical signs of CTD: anti-nuclear antibodies, cryoglobulinemia, electrophoresis of blood proteins, antiphospholipid antibodies and if previous tests are negative JAK-2 mutation research.

After investigations if UEDI remains idiopathic, an annual monitoring during, at least, 2 years could be realized.

Since UEDI with SSc and TAO had shown more recurrence, when an idiopathic UEDI present a recurrence, a search for the anti-nuclear antibody should be performed again. This search should be associated with careful clinical interrogation on cannabis-abuse and tobacco use as investigating for TAO.

5. Conclusion

This study described a large cohort of UEDI and showed that cardio-embolic diseases are the highest occurring aetiology. This study also found that iatrogenic cause of UEDI was frequent and increased by the use of vasopressor drugs and multiplication of endoarterial procedures. The midterm follow-up showed: UEDI associated with SSc had a poor local prognosis and DICE presented poor general prognosis. UEDI with SSc and TAO had more recurrence. That is why, when idiopathic UEDI shows recurrence, those aetiologies have to be researched as a priority. A prospective study of idiopathic UEDI and their clinical evolution should be performed to validate proximity to DICE in a larger cohort.

References

[1] Sharp CA, Akram Q, Hughes M, et al. Differential diagnosis of critical digital ischemia in systemic sclerosis: report of five cases and review of the literature. Semin Arthritis Rheum 2016;46:209–16.
[2] Kaznani N, Falatko J, Neupane S, et al. Calciphylaxis presenting as digital ischemia. Intern Emerg Med Jun 2015;10:529–30.
[3] Woei-A-Jin FJSJ, Tamsma JT, Khoe LV, et al. Lymphoma-associated paraneoplastic digital ischemia. Ann Hematol févr 2014;93:335–7.
[4] Paw P, Dharan SM, Sackier JM. Digital ischemia and occult malignancy. Int J Colorectal Dis 1996;11:186–7.
[5] McNally MM, Univers J. Acute Limb Ischemia. Surg Clin North Am oct 2018;98:1081–96.
[6] Bae M, Chung SW, Lee CW, et al. Upper limb ischemia: clinical experiences of acute and chronic upper limb ischemia in a single center. Korean J Thorac Cardiovasc Surg août 2015;48:246–51.
[7] Carpentier PH, Guillot JL, Hatron PY, et al. Nécroses et artériopathies digitales. J Mal Vasc sept 2005;30:29–37.
[8] Senet P. Diagnostic des acrosyndromes vasculaires. Ann Dermatol Vénéroléo août 2015;142:513–8.
[9] Le Besnerais M, Miranda S, Cailleux N, et al. Y. Digital ischemia associated with cancer: results from a cohort study. Medicine (Baltimore) 2014;93:e47. doi:10.1097/MD.0000000000000047.
[10] Marie I, Hervé F, Primard E, et al. Long-term follow-up of hypofenar hammer syndrome: a series of 47 patients. Medicine (Baltimore) nov 2007;86:334–43.
[11] Tolosa-Villéla C, Morera-Morales ML, Simeón-Aznar CP, et al. Digital ulcers and cutaneous subsets of systemic sclerosis: clinical, immunologi-cal, nailfold capillaroscopy, and survival differences in the Spanish RESCLE Registry. Semin Arthritis Rheum 1 2016;46:200–8.
[12] Marchal A, Mahé E, Sin C, et al. Acute finger ischemia: a retrospective study of 13 patients. Ann Dermatol Vénéroléo mai 2015;142:332–9.
[13] Keo HH, Umer M, Baumgartner I, et al. Long-term clinical outcomes in patients diagnosed with severe digital ischemia. Swiss Med Wkly 2011;141:w13139. doi:10.4414/smw.2011.13139.
[14] Skeik N, Soo-Hoo SS, Porten BR, et al. Arterial embolisms and thrombosis in upper extremity ischemia. Vasc Endovascular Surg août 2015;49:100–9.
[15] Sáez-Comet L, Simeón-Aznar CP, Pérez-Conesa M, et al. Applying the ACR/EULAR systemic sclerosis classification criteria to the spanish scleroderma registry cohort. J Rheumatol déc 2015;42:3237–31.
[16] Mills JL. Sr. Buerger’s disease in the 21st century: diagnosis, clinical features, and therapy. Semin Vasc Surg 2003;16:179–89.
[17] Cailleux N, Marie I, Lecomte F, et al. L’ischémie digitale: une affaire d’interistès. À propos de 96 observations. Rev Medécine Interne juin 1999;20:76.
[18] Vayssairat M, Fiessinger JN, Housset E. Les nécroses digitales du membre supérieur: 86 cas. Press Med 1977;931–4.
[19] Cailleux N, Levesque H, Gilbert P, et al. Les nécroses du membre supérieur en dehors de la sclérodermie. Etude rétrospective à propos de 45 cas. J Mal Vasc 1994;19:22–6.
[20] Abdallah M, Hamzaoui S, Larbi T, et al. Proﬁl étiologique des nécroses digitales des membres supérieurs: analyse de 25 observations. J Mal Vasc févr 2010;35:12–6.
[21] Taquin H, Pharaon M, Del Guicicce P, et al. Iatrogenic digital ischemia in a child. Ann Dermatol Venerol depuis 1995;142:76–7.
[22] Neal JM. Iatrogenic digital ischemia. Ann Emerg Med mars 1986;15:382–3.
[23] Ersek RA. Ischemic necrosis and elastic net bandages. Tex Med juill 1982;78:47–9.
[24] Miller TA, Haftel AJ. Iatrogenic digital ischemia. West J Med févr 1975;122:183–4.
[25] Linnemann B, Erbe M. Raynaud’s phenomenon and digital ischaemia–pharmacologic approach and alternative treatment options. VASA Z Gefasskrankheiten 2016;45:201–12.

[26] Herrick AL. Contemporary management of Raynaud’s phenomenon and digital ischaemic complications. Curr Opin Rheumatol nov 2011;23:555–61.

[27] Hughes M, Murray A, Denton CP, et al. Should all digital ulcers be included in future clinical trials of systemic sclerosis-related digital vasculopathy? Med Hypotheses Juill 2018;116:101–4.

[28] Colen DL, Ben-Amotz O, Stephanie T, et al. Surgical treatment of chronic hand ischemia: a systematic review and case series. J Hand Surg Asian-Pac Vol sept 2019;24:359–70.

[29] Mortier P, Schoofs M, Leps P, et al. Acute digital ischemia: a microsurgical emergency. Ann Chir Plast Esthet avr 2001;46:84–8.

[30] Ben Hammamia M, Ben Mrad M, Mleyhi S, et al. Revascularization delay and complications in acute upper limb ischemia. J Med Vasc mai 2019;44:194–8.