

## Original Article

# Limb gangrene: What is the best initial approach? A problem with serious controversy among rheumatologists

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**Abstract.** Critical ischemia of any organ is potentially the most devastating condition threatening all living organs. Gangrene or necrosis of organs is a common problem in routine clinical practice that mostly directed initially to surgical departments due to emergent nature of condition in nearly all cases with one exception of myocardial ischemia or infarction. Basic mechanism for non-traumatic vascular compromise is rather similar in nearly all organs however interestingly clinical approach is highly different in diverse clinical settings. Rather a thorough medical approach is as critical as debridement and revascularization techniques in order to diagnose and treat ongoing underlying pathologies. In this report we analyzed all different approaches of several rheumatologists in a real case scenario of unilateral foot gangrene. In this study, using e-mail questionnaire contacts, we sent the medical history of our patient with unilateral foot gangrene together with predesigned short questions and asked the opinions of 50 experienced rheumatologists from several parts of the world regarding initial management plan to handle the case. The responses were collected and analyzed. Twenty-six physicians (52%) responded of whom 22 (84%) suggested administration of heparin. Thrombolytic therapy was recommended by 3 (11.5%). There were many diverse ideas about starting intravenous (IV) steroid pulse: 15 (57.6%) recommended steroid pulse and 7 (27%) discouraged it. Two rheumatologists believed that this case is actually a surgical case and should not be handled in rheumatology service. We concluded that there is a serious controversy among rheumatologists regarding the management of patients with acute limb ischemia. Also, we suggest that in all uncertain vascular compromise, considering early institution of anti-inflammatory, anti-thrombotic therapies along with vasodilators could be a rational initial approach until further information is obtained from tissue biopsy and full panel laboratory investigation.

**Key words:** Critical ischemia, gangrene, vascular insufficiency, infarction, inflammation, necrosis, peripheral arterial disease

## Introduction

Critical ischemia of any organ may be due to breakdown of several defense barriers leading to gangrene or necrosis of individual organs. Other than external and traumatic factors, possible mechanisms of this catastrophic state could be in-situ bland or inflammatory thrombus, vasospasm, atherosclerosis, athroemboli, vasospasm, air emboli, vasculitides and in very rare instances vascular infiltration such as amyloidosis [1, 2]. All of these etiologies are basically a medical condition and a team approach should be considered in near all cases.

Tissues are impending to necrosis just minutes after acute ischemia. Based on possible mechanism of occlusion, very early medico-surgical intervention is advised to restart vital blood flow to the damaged organ [3]. Gangrene or necrosis of organs is a common problem in routine

clinical practice that mostly directed initially to surgical departments due to emergent nature of condition in near all cases with one exception; myocardial ischemia or infarction.

In most instances the prominent mechanism would be evident base on medical history; for example chronic ischemia in a man with heavy cigarette smoking is most probably due to highly inflammatory thrombosis in setting of thromboangitis obliterans (TAO), or acute ischemia of toes (blue toe syndrome) after surgical manipulation of aortic wall in an old man is highly predictive of athroemboli as the culprit mechanism. Similarly, subacute ischemia of an organ in setting of preexisting known connective tissue diseases also is highly indicative of secondary vasculitis even in the absence of documented vascular pathology. A vascular event in a rather young

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**Figure 1** Necrotic forefoot in the present case

person and negative history and classic risk factors merits more attention to the underlying mechanism other than atherosclerosis. Inflammatory mechanisms may have some prominent role in this regard. Surgical debridement of a necrotic tissue is not the sole task of health care providers in case of an organ necrosis. Rather, a thorough medical approach is as critical as debridement and revascularization techniques in order to diagnose and treat ongoing underlying pathologies.

Here we designed a research endeavor on a single challenging case of limb gangrene to evaluate different ideation and practice among rheumatologists.

### Material and Method

Using e-mail contacts, we asked the points of view of 50 experienced rheumatologists (minimum 5 years in practice) from several parts of the world (USA, England, Switzerland and Middle East) regarding the initial management plan to handle such specific vascular case. Twenty-six physicians responded to our questionnaire. Their responses to the predesigned short questions were collected and the data were analyzed.

### Patient's medical history

The patient was a 22 years old man who had sought medical care about one month ago with chief complaint of left calf swelling and pain. With the diagnosis of compartment syndrome, he underwent fasciotomy in other center but pain and swelling persisted. After 4 to 5 days, his left toes slowly began to get ischemic. One week after admission to our center, the ischemia proceeded to overt gangrene of all his left foot toes and spread to his left mid-

foot (Fig. 1).

He had a suspicious past history of chicken pox and testis pain and swelling. He also had history of ankle pain two months ago. The patient was smoker and also had addiction to several kinds of illicit drugs, but he denied intravenous drug abuse. He had history of recent weight loss and myalgia and recurrent oral painful lesions. On physical examination his distal left lower limb pulses were absent.

Laboratory data were: WBC=10000/mm<sup>3</sup>, Hb=10.5 g/dl, MCV=80/fl, PLT=339000/mm<sup>3</sup>, Urea=32 g/dl, Cr= 1.1mg/dl, AST=45 IU/L, ALT=106 IU/L, ALP=406 IU/l, ESR=76 mm/h and CRP=24mg/dl.

Liver function tests were normal and HBsAg and HCVAb and HIVAb were negative. Cryoglobulinemia assay showed positive results with low titer. ANA, ANCA (c, p), C3, and C4, all were normal. Transthoracic echocardiography was normal.

Doppler sonography of left lower leg indicated that common and superficial femoral veins had some thrombosis but were patent. Deep femoral vein was occluded with clot. Arteries (up to proximal dorsalis pedis and posterior tibialis arteries) were normal.

Magnetic resonance angiography (MRA) of both lower limbs showed normal results up to detectable area by MRA. Distal arteries were not visible at the left side. Vascular histopathologic examination revealed the diagnosis of vasculitis.

Using e-mail contact, we sent the medical history of the patient together with a short questionnaire to 26 different rheumatologists from USA, England, Switzerland and Middle East. Regardless of any potential final diagnosis, we asked the participant rheumatologists to answer the following questions about initial therapeutic approach to this patient:

- 1) Do you start heparin?
- 2) Do you consider thrombolytic therapy?
- 3) Do you start IV pulse of steroid?
- 4) Do you discourage IV pulse steroid?
- 5) Do you start IV/oral cyclophosphamide?
- 6) Do you start broad spectrum antibiotics?
- 7) Do you start ASA and Trental (pentoxifylline) and calcium channel blocker (CCB)?
- 8) What is your further advice please?

### Results

There were diverse opinions among the responders as summarized in Table 1.

Of the 26 responders, 22 (84%) suggested the administration of heparin. Thrombolytic therapy was recommended by 3 (11.5%). There were many different opinions about starting IV steroid pulse: 15 (57.6%) recommended steroid pulse and 7 (27%) discouraged it. In addition, 34% (9 of 26) advocated the use of cyclophosphamide, 50% (13 of 26) recommended administration of broad spectrum antibiotics and administration of ASA was suggested by 18 (69%), but calcium channel blockers and Trental (pentoxi-

TABLE 1  
DETAILS OF THE OPINIONS OF THE RESPONDERS TO THE QUESTIONNAIRE

No.	Participating rheumatologists	Heparin	Thrombolytic therapy	Pulse steroid	Discourage IV pulse steroid	Cytosan	Antibiotics	*ASA *Trental *CCB	Comments
1	LSH	Yes	No	Strongly No	Yes	Strongly No	Yes	Yes	*Consider it as a vasculopathy NOT true vasculitis & R/O Beurger's
2	MA	Yes	No	Strongly Yes	No	Yes	Not mentioned	Not mentioned	I recommend combination treatment as a vasculitis
3	MB	Yes	Yes	Yes	No	Not mentioned	Not mentioned	Not mentioned	Search for hypercoagulable states
4	ZM	Yes	No	Yes	No	Yes	Yes	Yes	*R/O infection before starting IV pulse of steroid & endoxan. *R/O propable behcet disease or malignancy.
5	BY	Yes	Not Mentioned	Yes	No	Yes	Not mentioned	Yes	Start heparin pluse IV steroid & IV cyclophosphamide & continue with prednisolone & AS , warfarin & IV cyclophosphamide (monthly)
6	HR	Yes	No	Yes	No	Not mentioned	Yes	Not mentioned	*R/O endocarditis. *overall possibility for vasculitis in similar cases please?
7	ZZ	Yes	No	Yes	No	Yes	Yes	Yes	*vasculitis due to drug abuse.PAN?
8	SL	Yes	No	Yes		No	No	Yes No No	*add an SPEP,cryofibrinogen,and homocysteine screen to your workup *recommend obtaining a visceral angiogram with MRA or CTA)
9	ZR	Yes	No	Yes	No	No	Yes (if he is febrile)	Yes No No	*consider vasculitis after R/O injection at the grain region *MR angiography
10	FK	Yes	-	No	Yes	Yes	Yes	Yes Trental? No	*EMG may reveal mononeuritis multiplex which supports aggressive treating with cytotoxics. I prefer oral prednisolone
11	JF	Yes	Yes	No	Yes (no need)	No	No	No	*APS panel *stop smoking and other drugs.
12	FD	-	-	-	-	-	-	-	*It is not a rheumatology case, refer him to a vascular surgeon
13	OD	Yes	No	No	No	No	No idea	No	*APS panel and other hereditary hypercoagulation marker *I would start anticoagulation, after diagnosis is defined.
14	MA	Yes	No	No	Yes	No	Yes	Yes	*I would start lloprost.
15	BT	Yes	No	Yes	No	May be after lab	Yes	Yes	Alprostadil/illoprost+medrol pulse+heparin+CCB+pentoxifyllin+ASA and then CTX pulse when the lab results come through. *testicular Bx
16	AS	-	No	No	No	No	Yes	Yes	*some opioids have severe effects On vasculature as vasospasm(ergo...)or thrombosis tendency
17	AH	Yes	No	Yes	No	Yes	No	Yes	*we had a few cases of vasculitis following substance abuse(specially amphetamine).all of them were resistance to therapy.
18	BZ	Yes	No	Yes	No	Yes	No	Yes	Approach initially as vasculitis
19	AO	Not yet	No	Yes	Only if infection	No	Possibly	No harm	*could this be eosinophilic fasciitis?eosinophil count?biopsy result post surgery? *APS? *suggest MRI of leg
20	AF	Yes	No	Yes	Yes	No	No	Yes	*serology for antiphospholipid antibody syndrome and hematology consult.
21	M SH	-	-	-	-	-	-	-	No intervention,conservative management
22	AA	Yes	No	No	Yes	Not mentioned	No	Yes	*abdominal CT scan with contrast will be reseasonable for finding any cle for PAN
23	MBO	Yes	No	Yes	No	No	Yes	Yes	It should be considered as a medical vascular emergency until proved otherwise.
24	HS	No	No	No	Yes	No	No	No	It is not a Rheumatology case, refer him to a vascular surgeon
25	AD	Yes	No	Yes	No	No	No	Yes	
26	PF	Yes	No	Yes	No	Yes	Yes	Yes	Regardless of final diagnosis, Initial approach is with rheumatologic point of view in a setting of team work.

fylline) each by 12 (46%). Two pioneer rheumatologists believed that this case is actually a surgical case and should not be handled in rheumatology service. One of them suggested testicular biopsy

At our center, the patient received heparin: 1000 IU/h, oral warfarin 7.5 mg/daily, ASA 80mg/daily, intravenous pulsed methylprednisolone (total of 3000 mg), diltiazem 30 mg three times a day and broad spectrum antibiotics during his hospital stay. Afterward, the patient underwent amputation of gangrene foot.

The patient discharged after 10 days with oral prednisolone 15 mg/daily, ASA 80 mg/daily, calcium channel blocker and combination antibiotics. Pathologic investigation was compatible with vasculitis with marked infiltration of involved vessel wall by mononuclear cells without marked thrombosis. After about three months of systemic therapy and discontinuation of drug abuse, he has an uneventful course after about six months.

## Discussion

The present study was a teaching trial on a common problem in routine clinical practice which has serious controversy among rheumatologists. Acute organ ischemia is an urgent medico surgical condition necessitating early intervention in order to restore vital circulation [4]. In most cases only a few minutes to hours are considered golden time for salvage therapy [5]. Depending on etiology of arterial occlusion and elapsed time from initial vascular insult, therapeutic and further diagnostic approach and also prognosis could be quite different [4].

Several pathophysiologic mechanisms are involved in critical ischemia. Trauma, thrombosis, atherosclerosis, inflammatory thrombosis, wide spectrum of vasculopathies (e.g. amyloidosis or livedoid vasculopathy) and frank vasculitis are among the most important mechanisms. In some instances multiple mechanisms may be involved [6]. In known accidental and external trauma, early decompression and vascular anastomosis is the gold standard of management. The most debatable scenario belongs to apparently idiopathic vascular compromise which needs a multidisciplinary team to approach.

Rheumatologists, cardiovascular interventionists, vascular surgeons, and skilled radiologists are the leading team of treatment in most instances. It seems prudent that all vascular accidents should be an urgent condition until proved otherwise. The similar scenario in cardiovascular field is familiar to most practitioners. In recent era, almost all cases of acute coronary syndromes are handled as quickly as possible in an attempt to restore vascular patency or minimize infarct size (thrombolytic therapy or coronary angioplasty). This is very critical in case of the heart as one of vital organs in the body. It is clear that any delay in handling jeopardized cardiac musculature directly lead to poorer prognosis. Recently in most centers a similar urgent strategy is established for cerebrovascular accidents and a similar approach is advised. For acute vascular problem in vital organs (heart and brain) needed attention is

paid and a lot of advances occurred in these fields in recent years [7]. Thrombolytic therapy is mainstay of medical management in case of heart and brain vascular events. But with unknown reason it is not usually true for limb ischemia, intestine and eye vascular events for example are less subject to adequate comprehensive attention. In these setting most approaches are directed to atherosclerotic or thromboembolic events with surgical revascularization or anti-platelete therapies [8]. For idiopathic limb gangrene, amputation and conservative management to prevent subsequent septic events is the routine management while this is an impossible approach in brain or heart. We believe that all acute (and all other types of) organ ischemia merits individual critical diagnostic and therapeutic approach in somehow similar manner.

It seems that major reports dealing with critical ischemia are provided by surgical departments with some serious limitations in comprehensive understanding of emergency medical conditions. Vasculitides are among the culprit mechanisms which have potential ability to cause peripheral arterial disease (PAD) [9]. Systemic vasculitis may be the presenting feature of any vascular catastrophe and cerebrovascular accidents [10], its role in pathophysiology of PAD is underemphasized (<http://www.ucdmc.ucdavis.edu/vascular/diseases/cli.html>). This is very important because this kind of vascular diseases are potentially treatable and curable. Unfortunately due to over-emphasis on the issue of atherosclerosis, the term PAD automatically infers to the concept of atherosclerosis or less commonly thrombosis itself. While vasculitides in typical forms present with prominent systemic symptoms, some other forms have characteristic local patterns (<http://www.hopkinsvasculitis.org/vasculitis/symptoms-vasculitis/>) or are asymptomatic [11]. Many cases of vasculitides e.g. temporal arteritis remain undiagnosed until when post mortem autopsy results may disclose them. This could be true for cryoglobulinemic vasculitis in case of intravenous drug abuse [12]. Interestingly we did not find any original article or case report dealing with vascular pathology of a common vascular catastrophe i.e. diabetic foot. This may highlights the issue of underestimating facts behind the vascular events.

Controversy is acceptable in many subjects but it could be challenging when we have very diverse (and occasionally opposite) opinions approaching a single case. It reflects incomplete or different understanding of physicians regarding an emergency vascular medicine. Due to multiple drug abuse of unknown material (cannabis, opium, and newly advanced chemical drugs), if one considers possible levamisole-contaminated cocaine [13], the question of initiating systemic glucocorticoids or cytotoxic agents remain unanswered. On the other hand, low titers of cyoglobulinemia in such case and possible intravenous drug abuse and risk of hepatitis C virus contamination makes the problem even more complex. Moreover, the term "cannabis arteritis" is proposed and reported frequently by

some authors which in most cases were associated with cigarette smoking leading to a syndrome similar to TAO [14, 15]. History of cigarette smoking makes the diagnosis of TAO more likely on top of differential diagnoses. Anemia of chronic disease type along with raised erythrocyte sedimentation rate and CRP highly indicate an ongoing inflammatory process as the causative mechanism. The role of intravascular (albeit non-systemic) inflammation in TAO is evident. Some investigators used cytotoxic agents in handling of TAO with good results [16]. We also tried pulsed methylprednisolone for several cases of TAO with remarkable short course results (unpublished data). These data emphasizes on less addressed role of local inflammation (and anti-inflammatory management) in TAO. Zheng et al. well described panmural infiltration of neutrophils, lymphocytes and monocytes and immune complex in involved vessels in TAO [17]. While cessation of smoking remains the main strategy in treatment of patient with suspected or definite TAO, early medico-surgical intervention seems to be crucial to minimizing the infarct size or preventing subsequent vascular events.

One of the interesting points from the existing literature is the fact that most papers addressing limb gangrene are emerge from surgical departments. So they may suffer from a serious bias in understanding medical aspects of vascular medicine. Accordingly most approaches (and teaching guidelines) are pointed to anatomic vascular diversion or canulation of obliterated vessels instead of looking beyond atherosclerosis / thrombosis and treating potential underlying autoimmune conditions.

## Conclusion

Taking together, we can conclude that even in case of probable TAO, considering early institution of anti-inflammatory, anti-thrombotic therapies along with vasodilators could be a rational initial approach until further information is obtained from tissue biopsy and full panel laboratory investigation.

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## Conflict of Interest

The authors declare no conflict of interest.

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