Pressure Challenge Test and Histopathological Inspections for 17 Japanese cases with Clinically Diagnosed Delayed Pressure Urticaria

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Abstract

Delayed pressure urticaria (DPU) is characterized by deep dermal wheals that appear in response to a local continuous pressure. Although it has been reported to complicate as many as 40% of cases of Caucasian patients with chronic urticaria, no definitive cases of Asian/Japanese patients have been reported in English literature. Here, we identified 17 cases of DPU, among 540 Japanese patients with urticaria (3.1%), based on careful history taking, pressure challenge test and, ideally, skin biopsy. Twelve out of 17 patients (70.5%) who undertook pressure challenge testing, developed wheal and erythema in the area of pressure 1-12 hours later. Six out of 15 patients (40%) were positive for the autologous serum skin test (ASST). All cases were complicated with ordinary chronic urticaria, and all specimens of skin biopsies performed for 12 patients showed substantial eosinophil infiltration. All cases were resistant to antihistamines with or without other non-steroidal medications and eventually treated with 0.25-1.5 mg/day of betamethasone. However, 12 of them (70.6%) were able to cease steroid use because of cure or remission. For those cured or in remission, the duration of steroid administration and that from the onset to diagnosis was 11.2 ± 11.0 and 54.8 ± 60.2 months (mean ± SD), respectively. DPU may be identified as a relatively rare complication of Japanese patients with chronic idiopathic

urticaria. A proper diagnosis and a small amount of steroid may be beneficial for the treatment of DPU.

Keywords

Delayed Pressure Urticaria, Chronic urticaria, Pressure challenge test, eosinophil, steroid

Abbreviations

DPU: Delayed pressure urticaria, ASST: Autologous serum skin test

Introduction

Delayed pressure urticaria (DPU) is characterized by deep dermal wheals that appear in the continuously compressed region 30 minutes or several hours after the release of the compression. The wheals last for several hours or up to 3 days, and may accompany a burning sensation and/or pain rather than itching [11]. The effectiveness of antihistamines is low, and many cases of DPU require oral steroids to suppress symptoms [3]. Eosinophil infiltration is a histopathological feature of DPU, but the diagnosis of DPU is usually made based on careful history taking and, ideally, pressure challenge test as necessary [9]. In Europe, DPU has been reported to coexist in as many as 40% of chronic urticaria cases [2]. However, there are no definitive reports of Asian patients in this regard, except for a few case reports written in Japanese. We here report 17 Japanese cases of DPU who visited our institute from April, 2002 to June, 2009, with an analysis of their clinical and histological features.

Materials and methods

1) Subjects

In this study, 17 patients with DPU were studied retrospectively among 540 patients with urticaria

(age: 1-89 years old, mean age: 38.4 ± 19.6 years old, gender: 192 males, 348 females) referred to Hiroshima University Hospital from April, 2002 to June, 2009. DPU was diagnosed on the basis of at least two episodes of wheals that had appeared 30 minutes or several hours after the continuous local compression, and had been prolonged for more than 12 hours.

Skin biopsies were performed under oral and written informed consent in the manner approved by a committee of Hiroshima University Hospital, and pressure challenge test was performed under oral informed consent.

2) Clinical Examination

We conducted complete blood counts, biochemical examinations and skin biopsy, as necessary, of wheals that had appeared for several hours or longer. For pressure tests, we developed a device that was adjusted for 6 healthy adult Japanese individuals (2 males, 4 females) referring to the condition advocated by Kobza Black, et al [4]. The pressure test device consists of a perforated 50 cm x 50 cm acrylic flame, 1 kg weights, and a 1 kg steel rod with a diameter of 1.4 cm. A rod with weights was perpendicularly lowered through the acrylic flame on a patient's back as shown in (Fig. 1). We

performed pressure challenge tests for 17 cases by compressing their lower back skin with a pressure of 4 kg/ 1.5cm^2 for 15 minutes. Autologous serum skin test (ASST) was conducted as previously described [12]. We intradermally injected 50 μl of autologous serum, 20 μl of 10 μg/ml histamine as positive control and 50 μl of 0.9% sterile saline as negative control. The skin reaction was determined as positive if the serum-induced flare diameter was ≥ 5mm than saline control or larger than the flare induced by histamine at 30 min as reported before [8, 12].

3) Outcomes in response to medications

Patients were classified as "cure" if their urticarial symptoms resolved and never recurred without any further treatments for not less than six weeks, as "remission" if their symptoms never recurred with non-corticosteroid therapy, and as "amelioration" if symptoms were suppressed with therapies including corticosteroid for six weeks or longer, respectively.

Results

1) Clinical features

All of 17 cases diagnosed as DPU (age: 29-63 years old, mean age: 46.7 ± 11.8 years old, gender: 5 males, 12 females) had also suffered from chronic idiopathic urticaria which was characterized by relatively deep and spontaneously occurring wheals. The duration of each wheal was 12-72 hours (48.7 ± 17.7 hours, mean ± SD). The time from patients' first awareness of urticaria to the diagnosis of DPU was 55.9 ± 61.3 months (Table. 1). None of them showed apparently abnormal data in complete blood counts and common biochemical examinations.

2) Pressure challenge test

Six healthy adult Japanese individuals (4 males, 2 females) were challenged by rods with weights on 1.5 cm^2 areas of their backs. They could tolerate up to 4 kg in weight and 15 minutes in duration. Four of them felt largely uncomfortable when applied with a rod with 4 weights (5kg), or with 3 weights (4kg) for longer than 15 minutes. We therefore carried pressure tests with a rod with 3 weights ($4kg/1.5cm^2$) for 15 minutes on 17 patients with urticaria diagnosed as DPU based on their histories. Twelve of them (70.5%) developed a wheal and/or an erythema in the area of pressure 1-12 hours later (Fig. 2a). In four cases, the wheal enlarged over the compressed area (Fig. 2b).

3) Autologous serum skin test (ASST)

Six out of 15 patients who undertook ASST (40.0%) were determined as positive. This positive rate was similar to 30 out of 72 (41.6%) patients with chronic urticaria without DPU [12].

4) Histopathological inspection

All of 12 patients who undertook skin biopsies showed a moderate to strong infiltration of eosinophils with other inflammatory cells, such as neutrophils and lymphocytes, in the superficial perivascular area of the dermis (Fig. 3).

5) Treatments

All patients were treated by antihistamines either according to the manufacturer's recommended dose or higher doses, with or without other therapeutic drugs, such as montelukast, tranexamic acid and cimetidine. All cases were resistant to those treatments, and additionally administered oral steroid (betamethasone 0.25-1.5 mg/day). However, symptoms of three patients (17.6%) treated by medications

including oral steroid eventually resolved and they were able to discontinue all treatments (classified in "cure"). Symptoms in nine patients (52.9%) remitted and they continued treatments without oral steroid ("remission"), and the symptoms in the other five patients (29.4%) were improved with medications including oral steroid ("amelioration") (Table 1). Durations of steroid administration to the cured 3 cases were 28, 4, and 3 months, respectively. Periods of overall treatment by our team for these cases were 36, 20, and 8 months, respectively. Durations of steroid administration to the remitted 9 cases were from 1 to 36 months. The average duration of steroid administration in the cured or remitted cases was 11.1 ± 11.0 (mean ± SD) months (Table 1).

Discussion

We identified 17 cases of DPU among 540 Japanese patients with urticaria. All of them suffered from spontaneously occurring wheals as well as wheals induced by a pressure. The pressure challenge test evoked wheals in 12 out of 17 patients (70.5%), whereas all 12 patients inspected by skin biopsies showed marked eosinophil infiltration. A positive rate of ASST among patients with DPU, 40%, was almost similar to that among patients with chronic urticaria without DPU in our institute [12].

The frequency of DPU in our cases of urticaria, 3.1%, is much less than 40% reported by Barlow et al [2], who performed a pressure challenge test to all 135 cases of chronic urticaria, but similar to, or slightly larger than 2% reported by Champion [6]. We might have overlooked patients with DPU potentials without an apparent history of pressure associated wheals, because we had not performed the pressure challenge test for all patients with urticaria. However, we have likely revealed the maximal reactions of patients who received the challenge test, since the pressure employed in this study, 4 kg/1.5 cm^2 on patients' back for 15 min, was larger than previously reported ones. The pressure challenge test reported by Barlow et al. employed steel rods with 1.5 cm diameters and weights of 2.5 and 3.5 kg [2]. Pressure challenge tests, which were recently proposed by the EAACI/GA^{2}LEN/EDF/UNEV consensus panel, applied metal rods with 1.5 cm diameter and weights of 2.5 kg, or those with 6.5 cm diameter and weights of 5kg for 15 min onto the skin of forearm, back or anterior thighs [9].

On the other hand, all histological specimens from 12 patients clinically diagnosed as DPU revealed substantial eosinophilic infiltration regardless of results in the pressure challenge test. McEvoy [10] et al. reported the infiltration of eosinophils and the deposit of major basic protein inside and

outside of the cell in wheals of DPU. Moreover, various proteins in eosinophil granules, including major basic protein, secreted by eosinophil activation increase vascular permeability both via mast cell activation and by a direct effect on vessels [7]. Barlow et al reported that the expression of adhesion molecules, such as E-selectin, ICAM-1 and VCAM-1, increased in DPU, in 6 to 24 hours after a compression. They argued that the overexpression of such molecules may induce a dense cellular infiltration [1]. Taken together, marked eosinophil infiltration and their activation may be more important than the reproducibility of pressure challenge tests and reactions in ASST for both diagnosis and the pathogenesis of DPU.

Since all 17 cases of DPU in this study were diagnosed as a complication of chronic idiopathic urticaria, it may be necessary to characterize DPU as a special subtype of chronic urticaria rather than an independent disease entity. Five patients recognized that pressure-associated wheals continued longer than spontaneous ones, but no apparent differences of durations were recognized by the other 12 patients with DPU.

In the treatment of DPU, antihistamines were not sufficient by themselves to suppress wheal generation in accordance with previous publications. We observed partial remission of symptoms in 3

out of 17 cases by combinations of montelukast and second generation anti-histamines, as reported by Nettis et al. [11]. However, all of our patients, including these 3 patients, were not tolerable in spite of various combinations of medications except for steroids. Steroid administration for chronic urticaria is not generally recommended because of adverse effects. In fact, 5 out of 17 patients in our study had temporal side effects such as general fatigue, moon face, and diabetes. In the literature, various medications, such as dapsone, methotrexate, sulfasalazine, and nimesulide, have been tried for refractory DPU as well as steroid [5]. However, the duration of steroid administration in 12 patients in "cure" and "remission" of DPU was much shorter than the duration of their illness until the diagnosis (11.1 ± 11.0 months vs 54.8 ± 60.2 months; mean ± SD). Therefore, as far as DPU is concerned, steroid administration might not only suppress apparent symptoms, but also shorten the duration of the illness. To confirm the utility of steroids for DPU, a larger scale study is needed.

In conclusion, a diagnosis of DPU coexisting with chronic idiopathic urticaria should be considered important to determine reliable prognosis and the selection of appropriate treatments.

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Table 1

Demographical features and clinical characteristics of 17 patients with DPU

No	Age	Sex	Duration until diagnosis(months)	Chronic Urticaria	Duration of pressure induced wheal (hr)	Duration of spontaneous wheal (hr)	Pressure challenge test	ASST	Eosinophil infiltration	Period of treatment in our hospital (months)	Duration of steroid administration(months)	Outcome of steroid
1	62	M	48	+	24-48	24-48	−	+	+	36	28	cure
2	29	M	2	+	72	72	−	nd	+	20	4	cure
3	60	F	180	+	48-72	48-72	−	+	+	84	84	amelioration
4	30	M	48	+	48-72	48-72	+	−	+	18	18	amelioration
5	40	F	48	+	48-72	48-72	+	−	+	118	118	amelioration
6	41	F	4	+	24-48	12	+	+	nd	8	3	cure
7	53	M	120	+	48-72	48-72	+	+	nd	141	36	remission
8	49	F	84	+	24-48	12	+	−	nd	45	1	remission
9	41	M	14	+	24-72	24-72	+	−	+	21	21	amelioration
10	32	F	192	+	12	12	−	−	nd	32	14	remission
11	35	F	30	+	48-72	24	+	−	nd	28	13	remission
12	54	F	96	+	48-72	24	+	+	+	23	5	remission
13	36	F	2	+	12	1-2	+	−	+	18	18	amelioration
14	63	F	72	+	48-72	48-72	−	−	+	21	6	remission
15	54	F	4	+	48-72	48-72	+	+	+	24	16	remission
16	57	F	3	+	48-72	48-72	+	nd	+	7	4	remission
17	58	F	3	+	12-24	12-24	+	−	+	6	4	remission

ASST: autologous serum skin test nd: not done

Fig. 1

Device for pressure challenge test (4 kg/1.5 cm^2, for 15 minutes)

Fig. 2

After pressure challenge test, erythema continued, and wheals appeared on the test site several hours later. (a), typical wheal, (b), the wheal enlarged over the pressed area.

Fig. 3

Superficial intradermal perivascular infiltration in case 13 (H-E stain). (a), x100, (b), x400.

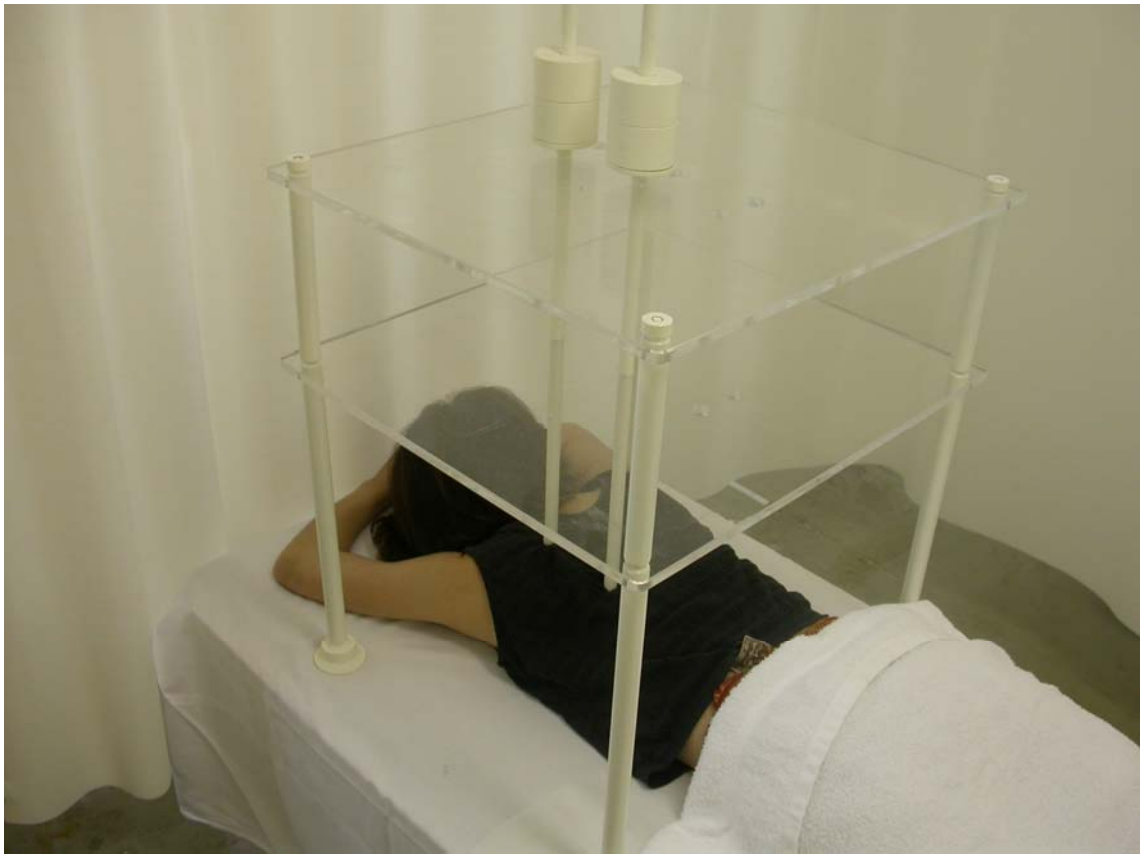

FIG 1

FIG 2a

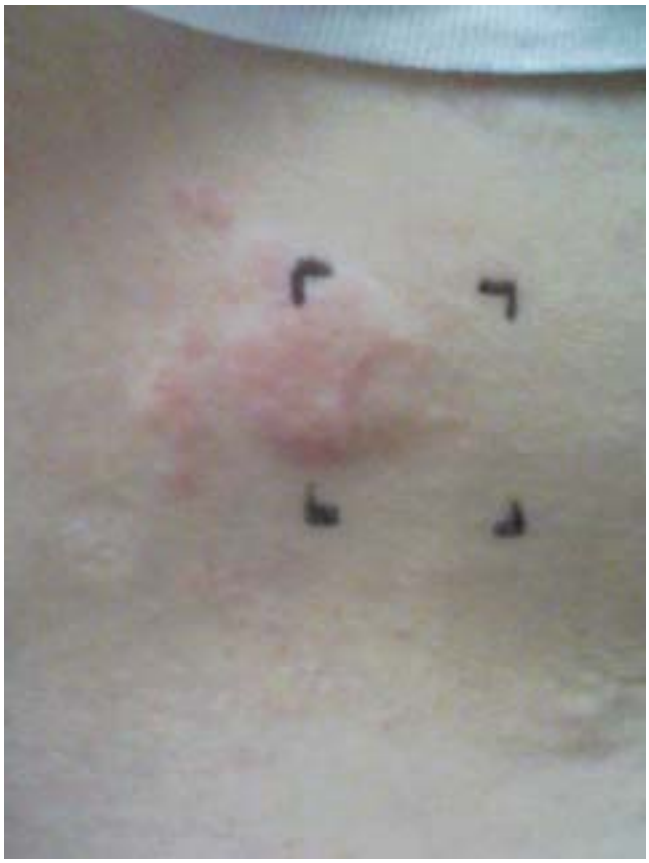

FIG 2b

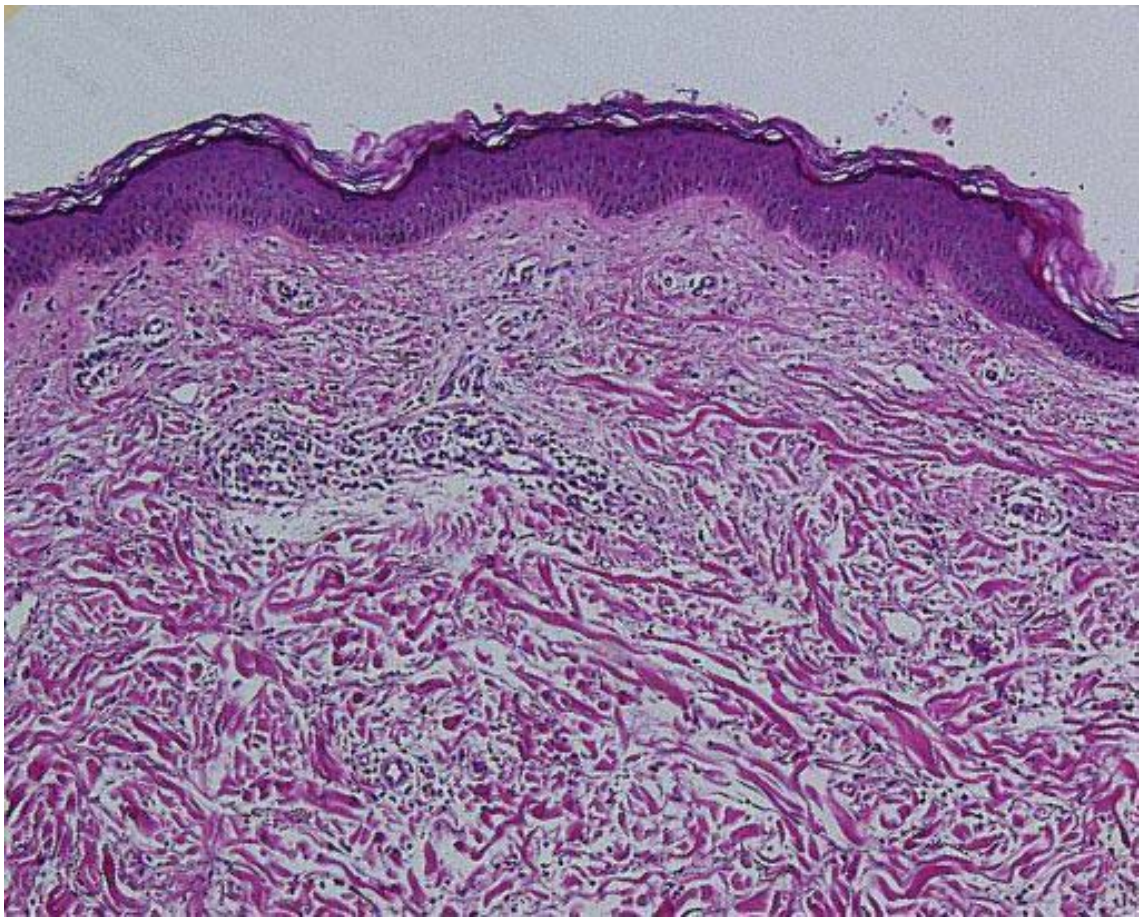

FIG 3a

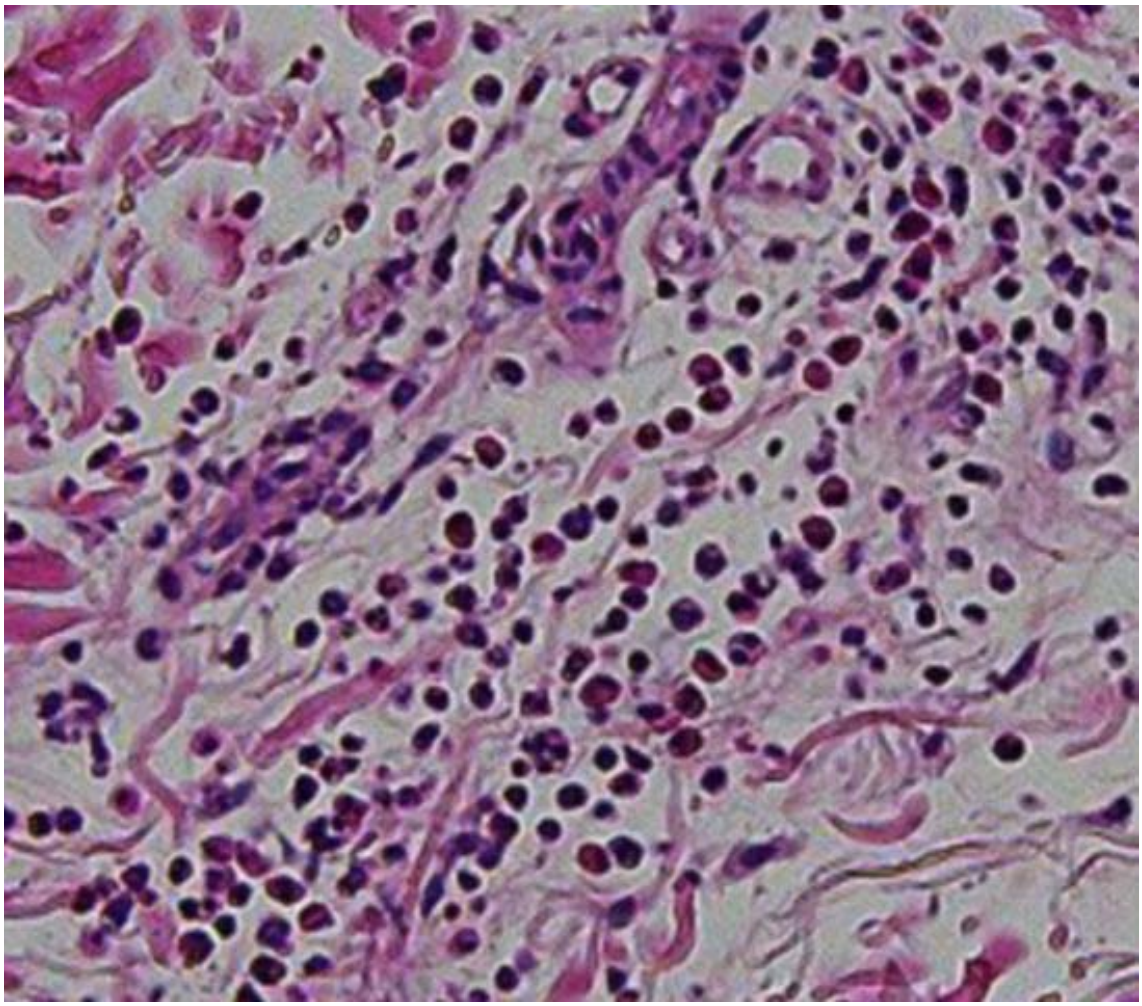

FIG 3b