Abstract
Tuberculous gummas are an unusual form of tuberculosis (TB) accounting for 1%–2% of all cutaneous TB cases. The aim of this article was to describe the epidemiological, clinical, bacteriological, immunological, and therapeutic features of this form upon a case report and a literature review. Forty-eight case reports were identified through a PubMed and Google Scholar search using the following keywords: “tuberculous gumma” and “metastatic tuberculous abscess.” Tuberculous gumma can occur at any age. Immunodepression is not a sine qua non condition to the development of the disease. Limbs are the most frequent site for gummas. Tuberculous gummas are associated to another location in only 73% of cases. The most frequent associated locations are lung, nodes, and musculoskeletal apparatus. Mantoux test is negative in 38% of cases. Skin stain is positive in 45% of cases and culture in 85% of cases. Giant epithelioid cell granuloma is present in 82.4% of cases. There is no universally accepted chemotherapy regimen for metastatic tuberculous abscesses. The classic 2RHZE/4RH is highly effective.

Keywords: Cutaneous tuberculosis, metastatic tuberculous abscesses, multifocal tuberculosis, tuberculous gumma

INTRODUCTION
Tuberculosis (TB) is an infectious disease due to Mycobacterium tuberculosis, characterized pathologically by necrotizing granulomatous inflammation. It usually involves the lung (=85% of cases), but other locations are current.[1] Cutaneous location is rare, which accounts only for 1.5% of extrapulmonary cases.[2]

Tuberculous gummas, also known as metastatic tuberculous abscesses, are unusual forms of cutaneous TB, with an incidence of only 1%–2% of all cutaneous TB cases.[3] Given the high prevalence of TB in many developing countries, these numbers are significant.

It is generally described in malnourished children and severely immunosuppressed adults, but its occurrence in immunocompetent individuals is possible.

We herein describe a patient with this rare and unusual cutaneous TB, as well as analyze all the available reports previously published in the medical literature. We describe the epidemiological, clinical, bacteriological, immunological, and therapeutic features of these cases.

There are limited case reports on tuberculous gummas and, to the best of our knowledge, the largest series comparing this cutaneous TB included only four cases.

METHODS
We performed a PubMed and Google Scholar search for tuberculous gumma using the following keywords: “tuberculous gumma” and “metastatic tuberculous abscess.” We identified 48 case reports, in addition to our own, and presented their main features in Table 1. The following three particular forms were excluded: chest wall gummas, as authors consider them a musculoskeletal form; paradoxical gummas developing during treatment of TB of other location; and sporotrichoid cutaneous TB, which has a particular way of expansion.
### Table 1: Literature review of tuberculous gummas

| Patients | Age | Gender | Site of gummas | Ulceration | Evolution time at diagnosis | HIV status | Significant comorbidities | Extra skin locations | Mantoux (or IFN-γ -releasing assay) | Skin stain/culture | Pathology | Treatment regimen | Total treatment duration (months) | Outcome |
|----------|-----|--------|----------------|------------|-------------------------------|------------|---------------------------|---------------------|---------------------------------|-----------------|-----------|-----------------|-------------------------------|---------|
| Amnaoui et al., 2015[3] | 19 | Male | N/A | N/A | N/A | None | Lung | 3+1 | Skin stain/culture | GECG with caseating | 2RHZE/7RH | 9 | N/A | Favorable |
| | 32 | Male | N/A | N/A | N/A | None | Lung, Osteo-arterial | GECG with caseating | 9 | |
| | 22 | Male | N/A | N/A | N/A | None | Lung, Osteo-arterial | GECG with caseating | 9 | |
| | 22 | Female | N/A | N/A | N/A | None | Lung, Osteo-arterial | GECG with caseating | 9 | |
| Bachmeyer et al., 2007[4] | 33 | Female | Thigh Leg Forearm Buttock Foot Elbow Lumbar (2) | + | 10 months | None (pregnancy) | Muscular Bone | - | Skin stain/Culture+ PCR- | GECG with eosinophilic necrosis | N/A | N/A | Favorable |
| | 87±1,4 | Female | Lumbar (2) | N/A | N/A | N/A | Nodal (2) | + (2) | Skin stain+ (2) Culture+ (2) | GECG with caseating | 6HR/2Z | 8 | N/A | |
| | 87±1,4 | Female | Nodal (2) | N/A | N/A | N/A | Nodal (2) | + (2) | Skin stain+ Culture+ | GECG with caseating | N/A | 12 | Favorable |
| Chaudhry et al., 2013[5] | 35 | Male | Scalp Buttock | - | 3 months | None | Lung, Cerebral Spinal Osteo-arterial Muscular | N/A | Skin stain+ | GECG with caseating | 3RHZE/9RH | 12 | Favorable |
| | 74 | Female | Hand Knee | + | 6 months | None | Nodal INF-γ+ | N/A | Skin stain N/A | GECG with caseating | N/A | N/A | Favorable |
| Poisnel et al., 2016[6] | 28 | Male | Hand | - | N/A | N/A | Chest wall Lung | - | Skin stain+ Culture+ | GECG with caseating | 2RHZE/7RH | 9 | Favorable |
| Bassir et al., 2014[7] | 72 | Female | Abdomen | + | N/A | N/A | Granulomatous hepatitis on corticosteroids and purinethol Gingival Nodal Lung Urogenital | N/A | Skin stain+ Culture+ | GECG with caseating | N/A | N/A | Favorable |

Contd...
| Patients | Age | Gender | Site of gummas | Ulceration time at diagnosis | Evolution time at diagnosis | HIV status | Significant comorbidities | Extra skin locations | Mantoux (or IFN-γ-releasing assay) | Skin stain/ pathomy | Treatment regimen | Total treatment duration (months) | Outcome |
|----------|-----|--------|----------------|-----------------------------|-----------------------------|-----------|--------------------------|---------------------|-------------------------------|---------------------|--------------------|-----------------------------|---------|
| Rodriguez-García et al., 2012[10] | 75  | Female | Shoulder       | +                           | 5 months                    | N/A       | Hydronephrosis Bronchiectasis | None                | N/A                           | GECG                | N/A                | N/A                         | N/A     |
| Ali Chaudhry and Al-Solaiman, 2013[11] | 21  | Male   | Superior limb  | -                           | N/A                         | -         | Substance abuse Lung Chest wall Nodal | GECG                | N/A                           | N/A                | N/A                | N/A                         | N/A     |
| Casas et al., 2003[12] | 77  | Female | Universal (trunk) | +                           | N/A                         | N/A       | Colic adenocarcinoma Nodal Mammary | Skin stain+ Culture+ | N/A                           | RHZE                | 9                  | Favorable                  |         |
| Espinosa-Lara et al., 2016[13] | 18  | Male   | Shoulder       | +                           | 6 weeks                      | -         | None Lung | Skin stain+ Culture+ | GECG                | N/A                           | RHZE                | N/A                | Favorable                  |         |
| Abdou et al., 2013[14] | 45  | Male   | Buttocks       | +                           | 6 months                     | N/A       | None None | Skin stain+ Culture+ | GECG                | N/A                           | N/A                | N/A                | N/A                         |         |
| Maroñas-Jiménez et al., 2015[15] | 57  | Female | Thigh          | +                           | 1 month                      | +         | CD4: 22/mm³ Nodal | Skin stain+ Culture+ | GECG                | RHZE                | N/A                | Favorable                  |         |
| Shukla et al., 2011[16] | 5   | Male   | Both cheeks    | -                           | 5 months                     | -         | None Spinal | Skin stain+ Culture+ | GECG                | 2RHZE/7RH            | 9                  | Favorable                  |         |
| Sezgin et al., 2008[17] | 5   | Female | Neck Elbow finger Foot | -                           | 7 months                     | -         | None Bone | Skin stain+ Culture+ | GECG                | 2RHZE/16RH           | 18                 | Favorable                  |         |
| Dekeyzer et al., 2013[18] | 26  | Male   | Thigh          | -                           | 9 months                     | -         | None Nodal | Skin stain+ Culture+ | GECG                | N/A                           | RZE + moxifloxacin | 12                 | Favorable                  |         |
| Silva et al., 2013[19] | 33  | Male   | Thigh          | +                           | 2 months                     | -         | Polymyositis On prednisone and MTX History of pulmonary tuberculosis 1 year ago | None                | N/A                           | Skin stain+ Culture+ | 2RHZE/4RH           | 5               | Favorable                  |         |

Contd...
## Table 1: Contd...

| Patients                      | Age | Gender | Site of gummas | Ulceration | Evolution time at diagnosis | HIV status | Significant comorbidities | Extra skin locations | Mantoux (or IFN-γ-releasing assay) | Skin stain/culture | Pathology | Treatment regimen | Total treatment duration (months) | Outcome |
|-------------------------------|-----|--------|----------------|-------------|----------------------------|------------|---------------------------|---------------------|------------------------------------|-------------------|------------|-------------------|----------------------------------|---------|
| Marcoval and Alcaide, 2013[20] | 48  | Female | Leg            | +           | 2 months                   | N/A        | N/A                       | Cerebro-meningeal  | -                                  | N/A               | N/A        | N/A               | N/A                             | Died     |
|                               | 62  | Female | Trunk          | +           | 1 year                     | -          | History of nodal tuberculosis | Nodal Mammary     | N/A                               | N/A               | N/A        | N/A               | N/A                             | Died     |
|                               | 47  | Female | Universal      | +           | 2 months                   | N/A        | None                      | None               | +                                  | N/A               | N/A        | N/A               | N/A                             | Favorable |
| Dash et al., 2012[21]         | 8   | Male   | Foot Retroauricular | +       | N/A                       | -          | None                      | None               | +                                  | GECG with caseating | RHZE     | N/A               | 6                                | Favorable |
| Sharma et al., 2014[22]       | 11 months | Male | Thigh          | -           | 8 months                   | -          | None                      | None               | +                                  | GECG with caseating | PCR+     | N/A               | Absence of granuloma              | N/A      | Favorable |
| Jean et al., 2012[23]         | 30  | Male   | Lumbar         | -           | 1 month                    | -          | None                      | None               | N/A                               | Absence of granuloma | N/A      | 6                  | Favorable |
| Matsuura-Otsuki et al., 2016[24] | 62  | Female | Abdomen        | -           | <4 months                  | -          | Diabetes mellitus type 2  | Lung Muscular Digestive Urogenital | N/A                             | RHZE     | N/A               | Favorable |
| Kato et al., 2014[25]         | 45  | Female | Forearm        | -           | N/A                       | -          | None                      | Pulmonary military tuberculosis | N/A                             | N/A      | 6                  | Favorable |
| Almagro et al., 2005[26]      | 44  | Male   | Foot           | -           | 6 months                   | -          | None                      | Lung Bone          | +                                  | GECG with caseating | 2RHZ/12RH | 14                 | Favorable |

*AOSD* hyperinflammatory state; MAS, methylprednisolone; MTX, methotrexate; MAS*†* simultaneous with multifocal tuberculosis; **Dash** et al., 2012[21] **Marcoval and Alcaide**, 2013[20] **Jean**, 2012[23] **Kato**, 2014[25] **Sharma** et al., 2014[22] **Matsuura-Otsuki** et al., 2016[24] **Almagro** et al., 2005[26] **Dash** et al., 2012[21]
### Table 1: Contd...

| Patients                  | Age  | Gender | Site of gummas | Ulceration time at diagnosis | HIV status | Significant comorbidities | Skin stain/ culture | Pathology                             | Treatment regimen | Total treatment duration (months) | Outcome                  |
|---------------------------|------|--------|----------------|-------------------------------|------------|--------------------------|--------------------|---------------------------------------|-------------------|-----------------------------------|------------------------|
| Mehta et al., 2015[27]    | 20   | Female | Elbow          | -                             | N/A        | None                     | Lupus vulgaris     | GECG without caseating               | 2RHZES            | 8                                | Favorable                |
| Lakshmi and Gnaneshwar, 2002[28] | 19   | Female | Hand Foot elbow | -                             | 5 months   | None                     | Lung               | GECG with caseating                  | N/A               | N/A                              | Favorable                |
| Caksen et al., 2002[29]   | 3    | Female | Scalp Abdomen  | -                             | 4 months   | N/A                      | Lung               | GECG with caseating                  | RHS               | N/A                              | Favorable                |
| Petit et al., 1989[30]    | 58   | Male   | Ankle Hand Popliteal fossa Cheek Thigh Hand Shoulder Flank | N/A | N/A | - | Gout on allopurinol | Lung Nodal | Skin stain- Culture+ | N/A                | N/A                              | Favorable                |
| Abdi et al., 2011[31]     | 40   | Female | Elbow          | -                             | 5 years    | None                     | None               | Skin stain- Culture+ | 2RHZE/4RH       | 6                                | Favorable                |
| Attia, 2006[32]           | 23   | Male   | Wrist          | +                             | N/A        | - | Pulmonary tuberculosis 3 years ago | Nodal | Skin stain- Culture+ | N/A                | 3RHZE/RH                  | N/A                    |
| Kalaria et al., 2000[33]  | 72   | Male   | Periam Perinium | +                             | N/A        | - | Nodal lymphoma simultaneously | None | Skin stain- Culture+ | N/A                | RHZE                    | N/A                    |
| Parker and Babu et al., 2013[34] | 24   | Male   | Wrist          | +                             | 2 months   | - | None | Lung N/A | Skin stain- Culture+ | N/A                | RHZE                    | N/A                    |
| Maejima et al., 2007[35]  | 77   | Female | Knee           | -                             | N/A        | - | ITP ‡ on prednisone 15mg/j | Pulmonary miliary tuberculosis | GECG with caseating | RHE               | 12                                | Chronic renal failure after initial extending of lesions |
| Vidal et al., 2001[36]    | 88   | Male   | Wrist          | +                             | 2 years    | - | Pulmonary tuberculosis 45 years ago Asthma | None | Skin stain- Culture+ | GECG               | 2RHZ/4RH                  | 6                                | Favorable                |
| Difonzo et al., 2006[37]  | 40   | Female | Thigh          | +                             | 8 months   | - | None | Nodal | Skin stain- Culture+ | N/A                | 2RHZ/4RH                  | 6                                | Favorable                |
Machan, et al.: Features of tuberculous gummas

Table 1: Contd...

| Patients | Age | Gender | Site of gummas | Ulceration | Evolution time at diagnosis | HIV status | Significant comorbidities | Extra skin locations | Mantoux (or IFN-γ-releasing assay) | Skin stain/culture | Pathology | Treatment regimen | Total treatment duration (months) | Outcome |
|----------|-----|--------|----------------|------------|-----------------------------|------------|--------------------------|----------------------|---------------------------------|-----------------|-----------|----------------|-----------------------------------|---------|---------|
| Chen et al., 1996[38] | 38 Female | Buttocks | N/A | N/A | None | N/A | Culture+ | N/A | 9EHR | Favorable |
| | 32 Female | Elbows, Buttock, Thigh, Finger | N/A | N/A | None (prednisone intake suspected) | Lung | N/A | Culture+ | GECG with caseating | 2 HRZ/4HR | 6 Favorable |
| 56 Male | Elbow, Knee, Wrist, Hand | N/A | N/A | None | None | SLE | N/A | Culture+ | N/A | Favorable |
| 27 Female | Buttocks, Thighs, Popliteal fossa, 2 forearms | N/A | N/A | Complicated malarial infection 4 months previously | Chest wall | N/A | Skin stain+ | GECC | 4EHR/11 EHZ + ofloxacin | 15 Late improvement |
| Voigtlander et al., 2015[40] | 62 Male | Arm | + | N/A | Double-lung transplantation due to bullous emphysema on tacrolimus MMF and prednisolone | Lung | INF-γ- | Skin stain+ | GECG with caseating | 9RZE | 9 Favorable |
| Bounouar et al., 2011[41] | 19 Male | Ankle, Cheek | + | N/A | None | Lung | Osteo-articular | Skin stain+ | 2RHZE/7RH | 9 Favorable |
| Present case | 78 Female | Hand, Foot | - | 4 months | None | Sjögren syndrome Pulmonary tuberculosis 40 years ago | None | N/A | GECC with caseating | 2RHZE/4RH | 6 Favorable |

* AOSD, † MAS, ‡ ITP. AOSD: Adult-onset Still’s disease, MAS: Macrophage-activating syndrome, ITP: Idiopathic thrombocytopenic purpura, N/A: Not available, GECG: Giant epithelioid cell granuloma, HCQ: Hydroxychloroquine, SLE: Systemic lupus erythematosus, MTX: Methotrexate, PCR: Polymerase chain reaction, INF-γ: Interferon-gamma, INH: Isoniazid
CASE REPORT

A 78-year-old woman presented with progressive swelling of the dorsum of the right hand and foot of 4 months’ duration. She was on prednisone 30 mg/day for Sjögren syndrome. The patient had suffered from pulmonary TB 40 years ago and had been treated and cured. In fact, she did not have any constitutional symptoms. On examination, a nontender, fluctuant, soft swelling, involving dorsum of the right hand and foot was visible [Figure 1]. No similar lesions were seen elsewhere.

Laboratory investigations revealed reduced hemoglobin (10.8 g/dl), high erythrocyte sedimentation rate (80 mm/l h), and an elevated C-reactive protein.

X-ray of the chest and extremities was normal. Biopsy of the mass with bacteriological and pathological examination showed acid-fast bacilli and classical tuberculous granulomas with caseation necrosis. Culture was also positive.

The diagnosis of tuberculous gumma was proved, and chemotherapy was initiated, including isoniazid 300 mg (H), rifampin 450 mg (R), ethambutol 800 mg (E), and pyrazinamide 500 mg (P) daily initially for 2 months (RHEP), followed by a 4-month course of two drugs (HR). The patient had remarkable improvement with rapid regression of the swelling without fistulization.

RESULTS

We identified 49 published reports, including our own, of tuberculous gummas, occurring alone or in association with other tuberculous locations. Table 1 summarizes the main characteristics of these cases.

The average age of the patients was 42.3 years, with extremes ranging from 11 months to 88 years. Fourteen patients (28.6%) were older than 60 years and 11 (22.4%) were older than 70 years. Only five patients were less than 10 years. Male-to-female sex ratio was of 1. The delay of consultation was approximately 8 months.

All anatomic areas were involved, with predominance on limbs (80%). The upper limb was involved in 45% of patients and lower in 55% of cases with mentioned location. Trunk involvement was seen in 24% of patients. Only 13% had gummas of the neck and head.

Only one patient had HIV infection, but other proved conditions of immunosuppression such as intake of corticosteroids or immunosuppressants were present in eight patients (17.4%). Other conditions occasioning weakness of the immune system, such as malnutrition, substance abuse, pregnancy or cancers, or even elderly, were seen. Twenty-two patients (45%) were young adults without comorbidities, and 16 out of the 22 had multifocal forms. Six patients had a personal history of TB.

Forty-one percentage of the patients had one associated location and 23% had two associated locations, with multifocal forms accounting for at least three associated locations been present in 8% of cases. Tuberculous gumma can be an unique location of TB as was seen in 13 cases (27%), out of whom three had a history of pulmonary TB. Lung was the most frequent associated location (18 cases, with three miliary TB), followed by nodes (13) and musculoskeletal apparatus (11). Other sites are rare. Cerebromeningeal form was seen in two patients with severe clinical presentations.

Clinically, 31% of patients presented ulceration or fistulization. Nonfistulating gummas were seen in 69% of cases. The clinical aspect was not mentioned in seven cases.

The Mantoux test was fulfilled for 29 patients from whom 62% had a positive test and 38% had a negative test. Interferon-γ (IFN-γ) release assays were done in two cases, which came out to be positive in one case and negative in one case.

Skin stain was positive in <50% of patients (15 vs. 18). Culture was positive in 85% of cases (29 vs. 5). Polymerase chain reaction was done in only eight cases which was positive in 6 (75%) cases, which is in discordance with culture in some cases.

Giant epithelioid cell granuloma was present in 82.4% of cases (28/34). Caseation was seen in 21 cases (61.8% in total) and absent in 6 cases.

The five major antibacillar drugs (ethambutol [E], isoniazid [H], rifampin [R], pyrazinamide [Z], and streptomycin [S]) were used in different regimens. Ofloxacin and moxifloxacin were introduced in one case each, for rifampin-induced fever and an isoniazid-resistant strain, respectively. The treatment was administered for different durations. We consider only cases with isolated gummas without other location which can modify therapeutic attitude. Favorable outcomes were seen with all regimens, except for one case for which ofloxacin was used after rifampin-induced fever, in which the treatment was prolonged to 15 months with late response and final healing. A regimen of 6 months was used in five out of eight cases, regimen of 5 months in one case, and 9 months in one case.

DISCUSSION

TB is an universal health problem and is not only limited to third world countries. It has recently increased in developed
countries as well and, as a result, cutaneous TB has also been increasing.

Tuberculous gumma is still rare in developed countries, where lupus vulgaris and scrofuloderma are largely predominant.\footnote{42} It results from hematogenous spread of the mycobacterium from a primary focus during a period of impaired immunity. Our results suggest that tuberculous gumma can occur at any age, but with more prevalence in the elderly, probably due to a more prolonged exposition, a physiologic decrease in immunity, and the underlying diseases sometimes requiring immunosuppressant drugs.

Limbs are the most frequent site for gummas, especially thigh and buttocks. Location on the trunk is also usual. Abundant fat on these locations can bring an explanation. Immune depression is not a sine qua non condition to the development of the disease. An important part of patients are immunocompetent young adults.

Tuberculous gummas are isolated in a quarter of cases, demonstrating that gummas can occur by reactivation of ancient cutaneous foci upon an impaired immunity. However, an exploration to determine a second location is necessary. It must concern lung, nodes, and musculoskeletal apparatus, as those are the most frequent locations. A pulmonary miliary TB is possible, which must be tracked carefully, as it will change the therapeutic regimen.

Fistulization is late and, even with an average of 8 months’ delay of consultation, only 31% of patients have ulceration. Tuberculous gumma should be considered in patients with cold abscesses.

Mantoux test is of limited accuracy in the diagnosis of tuberculous gummas, as it is negative in 38% of cases. The number of cases using IFN-γ release assay is not sufficient to make a conclusion.

Skin stain lacks sensitivity and, in many occasions, only culture will resolve the problem. Herein, delay in culture is the major constraint. Giant epithelioid cell granuloma is highly specific and is present in 82.4% of cases. A biopsy should be undergone promptly if a tuberculous gumma is suspected and repeated if no granuloma is detected.

According to these data, tuberculous gummas are very heterogeneous and present with a wide variety of clinical and paraclinical presentations. They occur in a large profile of patients, whether with good cellular immunity status or not. M. tuberculosis is not always simple to trace on pus. Virulence of the bacilli is a factor to be kept in mind. All the available tests should be undergone to make the diagnosis, and culture is the most reliable examination.

There is no universally accepted chemotherapy regimen for metastatic tuberculous abscesses. The classic 2RHZE/4RH was highly effective, but less toxic and shorter regimens were also effective. May be in the future, with fulfillment of resistance tests more routinely, adapted regimens will be suitable.

Besides the lack of large series, this work can be considered of important help to better understand the clinical, bacteriological, and immunological characteristics of gummas. However, it is still limited by the heterogeneous aspect of the cohort and the small number of cases published.

**Conclusion**

Tuberculous gumma can occur at any age. Limbs are the most frequent site. Associated locations are present in 3/4th of cases. Lung, nodes, and musculoskeletal apparatus are the most frequent associated locations. Mantoux test is negative in 38% of cases. Skin stain is positive in <50% of cases. Culture is positive in 85% of cases. Giant epithelioid cell granuloma is present in 82.4% of cases. The classic 2RHZE/4RH is highly effective in the treatment of this form.

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**Conflicts of interest**

There are no conflicts of interest.

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