Case report of a clinically indolent but morphologically high-grade cutaneous mast cell tumor in an adult
Wardle, Claire L W; Oldhoff, J Marja; Diepstra, Arjan; Valent, Peter; Horny, Hans-Peter; Oude Elberink, Hanneke N G; Kluin, Philip M; Diercks, Gilles F H

Published in:
Journal of Cutaneous Pathology

DOI:
10.1111/cup.14088

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Case report of a clinically indolent but morphologically high-grade cutaneous mast cell tumor in an adult: Atypical cutaneous mastocytoma or mast cell sarcoma?

Claire L. W. Wardle1 | J. Marja Oldhoff2 | Arjan Diepstra1 | Peter Valent3,4 | Hans-Peter Horny5 | Hanneke N. G. Oude Elberink6 | Philip M. Kluin1 | Gilles F. H. Diercks4 ●

1Department of Pathology and Medical Biology, University Medical Centre Groningen, Groningen, The Netherlands
2Department of Dermatology, University Medical Centre Groningen, Groningen, The Netherlands
3Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria
4Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria
5Institute for Pathology, Ludwig-Maximilians University, Munich, Germany
6Department of Allergy and Immunology, University Medical Centre Groningen, Groningen, The Netherlands

Correspondence
Gilles F. H. Diercks, Department of Pathology and Medical Biology, University Medical Centre Groningen, Groningen, The Netherlands.
Email: g.f.h.diercks@umcg.nl

Funding information
Austrian Science Fund (FWF), Grant/Award Numbers: F4704-B20, P32470-B

Abstract
We present a case of an adult male with a solitary mast cell tumor of the skin with unusual nuclear pleomorphism and mitotic activity. The tumor was excised, recurred within 2 years, was reexcised after 4 years and did not recur >6 years after diagnosis. The tumor showed progressive cytonuclear atypia and a high mitotic and proliferation rate by Ki67-staining from the onset. No KIT mutations were identified in the tumor and bone marrow. Serum tryptase levels and a bone marrow aspirate and trephine biopsy were normal. Although the histomorphology of the skin tumor was consistent with mast cell sarcoma, the clinical behavior without systemic progression argued against this diagnosis. The tumor was finally considered as atypical mastocytoma, borderline to mast cell sarcoma. Currently, the patient is in close follow-up and still in complete remission.

KEYWORDS
adult, case reports, mast-cell sarcoma, mastocytoma, mastocytosis

1 | INTRODUCTION

Mastocytosis is a heterogeneous disease, characterized by expansion and accumulation of clonal mast cells. The disease may be limited to the skin (cutaneous mastocytosis), may be systemic (indolent, smoldering, aggressive, or leukemic) or rarely presents as a malignant solid tumor with destructive growth, known as mast cell sarcoma (MCS).1,2 Localized cutaneous mastocytoma mainly presents in prepubertal children, but is extremely rare in adults.1,3 The exact incidence is unknown.3 In the literature, only 14 cases of adult purely cutaneous mastocytomas have been reported.4-15

In cutaneous mastocytosis and indolent systemic mastocytosis, mast cells have round or oval nuclei and abundant metachromatic cytoplasm,1 or are spindle-shaped hypogranulated cells being referred...
as atypical mast cells type I. A third type of cytomorphology consists of mast cells with nuclear pleomorphism, including bilobation and/or multilobation; these cells are known as atypical mast cell type II or promastocytes.

In the literature, nine cases of benign mastocytosis or mastocytoma of the skin with type II atypia have been reported, including two adult cases. Although histomorphology raised concern about a malignant behavior, none of these patients showed systemic involvement or destructive growth, and after excision no recurrence was observed.

Here, we report on an atypical solitary mast cell tumor in a middle-aged patient, which in contrast to the other described cases recurred after excision, showed progressive cytological pleomorphism and an unusually high proliferation rate, but did not show any signs of clinical malignancy after more than 6 years of follow-up.

2 | CASE REPORT AND RESULTS

2.1 | Case report

In January 2014, a 44-year-old male presented with a solitary yellowish plaque on the skin of the right temple (Figure 1A, Table 1). The lesion had been stable for 5 months and was itchy upon touching. His case history reported a thin superficial spreading melanoma on the right upper leg in 2012 (the diagnosis being confirmed upon revision). There was no history of pediatric cutaneous mastocytosis.

Histopathological examination of a punch biopsy showed diffuse sheets of epithelioid cells in the dermis, without involvement of the epidermis or skin adnexa. The cells had abundant, pale eosinophilic, ashy to finely granulated cytoplasm, and contained no melanin pigment. The nuclei were slightly polymorphic, with mostly round and some oval forms. Spindle-shaped cells, and cells with irregularly shaped, bilobed and multilobed nuclei were sparse. There was a low, nonatypical mitotic activity, with up to one mitotic figure/mm². The Giemsa-stain highlighted the metachromatic granules and scant intermixed eosinophils. In this and later biopsies, immunohistochemistry was positive for CD117, tryptase (Figure 2B), and microphthalmia-associated transcription factor.

Other neoplastic conditions were excluded by immunohistochemistry using antibodies against S-100, Melan-A, HMB-45, SOX-10, pan keratin (CKAE1/3), p40, CD1a, and CD34. The CD30 stain showed a heterogeneous pattern with some strongly positive tumor cells. In the CD25-stain, there were a few positive cells. Neoplastic cells stained negative for CD2. Next generation sequencing analysis did not show mutations in KIT (including exon 17).

Physical examination disclosed normal results. Laboratory testing showed a normal serum tryptase level (2.9 μg/L, normal value <11.4 μg/L). No further staging procedures were performed.

An excision followed in July 2014. Histopathology revealed a similar picture compared to January 2014, with a slight increase of pleomorphic nuclei and mitotic activity (Figure 2A). In a hot spot, up to nine mitotic figures/mm² were found (Figure 2C). The Ki-67 proliferation index reached up to 29.5%. In addition to the well demarcated tumor bulk, the CD117 and tryptase highlighted perivascular and periadnexal continuation of small clusters of mast cells, including few pleomorphic mast cells, into the resection margins (Figure 2D).

2.2 | Provisional diagnosis

Based on histopathological studies and staging investigations, a provisional diagnosis of a mastocytoma was made, because of the clinical presentation of a solitary nodule without evidence of systemic disease, non-destructive growth and the low proportion of atypia.

2.3 | Clinical course in the follow-up

In June 2016, the patient returned with a recurrent papule. The lesion had grown back 3 months before and was itchy upon touching. Histopathology of the biopsy showed a morphology nearly identical to that seen in the biopsy of 2014, now with slightly more intermixed eosinophils. The Ki-67 proliferation index reached up to 17.9%. The blood tryptase level was still low (4.55 μg/L). Due to the lack of complaints, a wait and watch strategy was proposed.

In August 2018, another punch biopsy was taken of the plaque due to irritation and slowly increasing size of the lesion (Figure 1B).
Histopathological examination showed a similar picture, still without epidermal involvement or a destructive growth pattern. However, there was a marked increase in mast cells with pleomorphic nuclei. Again, only a few spindle-shaped cells were found. Mitotic activity was substantial, with up to 18 mitotic figures/mm², without atypical mitotic figures. In the Giemsa-stain, most neoplastic cells were hypogranulated. The Ki-67 proliferation index reached up to 33.5%.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Summary of the clinical course and laboratory, imaging, and histopathological characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>2014</td>
</tr>
<tr>
<td>Solitary plaque right temple. No other abnormalities</td>
<td>Recurrent solitary papule right temple. No other abnormalities</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
</tr>
<tr>
<td>Local excision</td>
<td>No (only punch biopsy)</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>Blood count</td>
<td>ND</td>
</tr>
<tr>
<td>Renal function</td>
<td>ND</td>
</tr>
<tr>
<td>Liver function</td>
<td>ND</td>
</tr>
<tr>
<td>LDH (n &lt; 248 U/L)</td>
<td>ND</td>
</tr>
<tr>
<td>Serum tryptase (n &lt; 11.4 μg/L)</td>
<td>2.9 μg/L</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>ND</td>
</tr>
<tr>
<td>Histopathology</td>
<td>ND</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>CT scan thorax</td>
<td>ND</td>
</tr>
<tr>
<td>MRI skull</td>
<td>ND</td>
</tr>
<tr>
<td>FDG-PET/CT scan</td>
<td>ND</td>
</tr>
<tr>
<td>Molecular analysis</td>
<td></td>
</tr>
<tr>
<td>NGS</td>
<td>No KIT mutation (skin lesion)³</td>
</tr>
<tr>
<td>Mutation specific PCR</td>
<td>ND</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td></td>
</tr>
<tr>
<td>CD117</td>
<td>Positive</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Positive</td>
</tr>
<tr>
<td>S100</td>
<td>Negative</td>
</tr>
<tr>
<td>MITF</td>
<td>Positive</td>
</tr>
<tr>
<td>CD25</td>
<td>Negative</td>
</tr>
<tr>
<td>CD2</td>
<td>Negative</td>
</tr>
<tr>
<td>CD30</td>
<td>Positive (heterogeneous)</td>
</tr>
<tr>
<td>Proliferation</td>
<td></td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>9/mm²</td>
</tr>
<tr>
<td>Ki67</td>
<td>29.5%</td>
</tr>
</tbody>
</table>

Note: The major criterion for mastocytosis is the presence of multifocal clusters of mast cells (≥15 mast cells in aggregates) in bone marrow and/or other extracutaneous organs. Minor diagnostic criteria include elevated serum tryptase level, abnormal mast cell CD25 with or without CD2 expression, presence of KIT D816V mutation, and more than 25% of mast cells with atypical morphology in bone marrow or other extracutaneous organs.²

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; LDH, lactate dehydrogenase; MITF, microphthalmia-associated transcription factor; MRI, magnetic resonance imaging; ND, not done; NGS, next generation sequencing; PCR, polymerase chain reaction; PET, positron emission tomography.

³Performed after reexcision of the tumor.

²NGS included analysis of exons 8, 9, 11, 13, 14, and 17.
In December 2018, reexcision with a wide local margin was performed. The histopathology was similar compared to previous studies, with a well demarcated lump containing predominantly pleomorphic mast cells (Figure 3A). Loose clusters of less atypical mast cells continued into the edges of the excision along the adnexa and vascular network, as in the previous excision. In a hot spot, 11 mitotic figures/mm² were found. The Ki-67 proliferation index was highly variable (<1% and in hot spots up to 25.3%) (Figure 3B).

The tryptase level remained low (4.37 µg/L). A bone marrow biopsy was performed in January 2019 and showed trilinear hematopoiesis with a slight increase in eosinophils. No mast cell aggregates or atypical mast cells were found. The bone marrow aspirate also did not show atypical mast cells, no co-expression of CD2 or CD25 on mast cells in flow cytometry, and no KIT D816V mutation. Postoperative magnetic resonance imaging of the skull did not show any residual mass. A computed tomography of the thorax did not show lung abnormalities or lymphadenopathy. Until October 2020 (last visit), no local recurrence or systemic involvement occurred.

3 | DISCUSSION

In the current case, atypical cutaneous mastocytoma and MCS are the main differential diagnostic considerations. The WHO classification defines cutaneous mastocytoma as “mostly pediatric lesions with sheets of mature looking mast cells … without cytological atypia, which enables the distinction from an extremely rare MCS of the skin” (Figure 3B); it defines MSC as “an extremely rare entity characterized by localized destructive growth of highly atypical mast cells.” In the registry of the European Competence Network on Mastocytosis, 2 out of 2985 adult patients (<0.1%) presented with MCS. There are 13 cases of MCS or MCS-like neoplasms in adults reported in the English literature, including cutaneous and extracutaneous forms. Additionally, there are five reported cases of systemic mastocytosis with sarcomatous growth of mast cells, all in adults and extracutaneous. All MCS cases showed extensive local destructive growth, “metastases” and/or secondary systemic involvement, mostly in form of an MCL.
In our case, some features consistent with MCS were present, that is, recurrence of the lesion, (progressive) cytologic atypia, and pronounced mitotic activity. However, the lack of invasive growth, absence of secondary systemic involvement, and the long-term survival in our patient did not fit with the highly malignant behavior of MCS. On the other hand, recurrent lesions are rare in mastocytoma. Of the 14 cases in the literature with adult mastocytomas, eight had a MCS. On the other hand, recurrent lesions are rare in mastocytoma. The long-term survival in our patient did not fit with the highly malignant behavior of MCS. Therefore, a more probable diagnosis is an atypical mastocytoma of the skin, borderline to a sarcoma. Because this is a mast cell tumor with unique features, the biopsy was performed for diagnostic purposes.33 However, in contrast to our case, mitotic figures were not present and recurrence of the lesion was not mentioned. On the basis of the above-mentioned features, we argue that the lesion should be diagnosed as an atypical mastocytoma of the skin, borderline to a sarcoma. Because this is a mast cell tumor with unique features, the biological behavior cannot be predicted. We believe that this case is an unusual clinical presentation.

ACKNOWLEDGMENTS

A. ter Elst, clinical molecular biologist in pathology at the UMCG, for interpretation of molecular tests. W. Blokx, dermatopathologist at the UMCU, for performing the CD25 and diagnosing the 2018 excision. A. Mulder, clinical chemist at the UMCG, for interpretation of the bone marrow aspirate flow cytometry and KiT mutation analysis of the bone marrow. The pathology departments of Diakonessenhuis Utrecht, St. Antonius Nieuwegein and University Medical Center Utrecht, The Netherlands, for sending material. P. V. was supported by the Austrian Science Fund (FWF), grant Nos. P32470-B and F4704-B20.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Gilles F. H. Diercks https://orcid.org/0000-0001-8053-216X

REFERENCES


**How to cite this article:** Wardle CLW, Oldhoff JM, Diepstra A, et al. Case report of a clinically indolent but morphologically high-grade cutaneous mast cell tumor in an adult: Atypical cutaneous mastocytoma or mast cell sarcoma? *J Cutan Pathol*. 2021;1–6. [https://doi.org/10.1111/cup.14088](https://doi.org/10.1111/cup.14088)