New Insights into Macular Type of Primary Cutaneous B-Cell Lymphoma: Extension of the Clinical and Histopathological Patterns

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Keywords
Macule · Patch · Primary cutaneous B-cell lymphoma · Follicle center-cell lymphoma · Marginal zone lymphoma

Abstract
Background: Primary cutaneous B-cell lymphoma (PCBCL) classically presents with papules, plaques, and nodules/tumors. Previous reports of PCBCL manifesting with macular lesions are scarce and focused on primary cutaneous follicle-center cell lymphoma (PCFCL). Objectives: The objective of this study was to report our experience with PCBCL presenting with erythematous macules. Methods: Patients with low-grade PCBCL manifesting with erythematous patches, diagnosed and managed between January 2000 through December 2019 at 2 tertiary cutaneous-lymphoma outpatient clinics, were included. Clinical data were retrospectively collected, and biopsy specimens of the macules, and if present of the typical nodular/tumoral lesions, were reviewed. Results: There were 14 patients, aged 16–67 years, 8 had PCFCL and 6 marginal zone lymphoma (PCMZL). All had 1–15 cm erythematous macules, mimicking: interstitial granuloma annulare/vascular tumors/early-stage folliculotropic mycosis fungoides, or presenting with figurate erythema or livedo reticularis-like/net-like pattern. In 3 patients, macules were the presenting lesions, in 2 as the sole manifestation, whereas in 12 patients, typical PCBCL lesions were observed during disease course. The macules showed in all, superficial and deep perivascular infiltrates, and in most, periadnexal infiltrates. Micronodules were observed in 11 specimens, with nodular infiltrates also observed in 4. B cells comprised the majority of the lymphocytes in only 4. Seven of 11 cases tested showed immunoglobulin heavy chain monoclonality. Conclusions: PCMZL and PCFCL may manifest with erythematous macules. Physicians should be aware of this unusual manifestation of low-grade PCBCL, which may represent a clinicopathological diagnostic pitfall.

Introduction

Primary cutaneous lymphomas (PCLs) are the second most common group of extranodal non-Hodgkin lymphomas. In the western world, 20–25% of all PCLs are B-cell neoplasms. The World Health Organization-European
Organization for Research and Treatment of Cancer (WHO-EORTC) classification recognizes three main types of primary cutaneous B-cell lymphoma (PCBCL): primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle-center cell lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type, and additional rare subtypes [1]. PCFCL and PCMZL are low-grade lymphomas that present typically as isolated, grouped/multiple erythematous-violaceous papules, or infiltrated-plaques/nodules in an asymmetric distribution, preferentially located on the head/neck and back (PCFCL), or on the trunk and extremities (PCMZL) [1, 2].

Unusual clinical manifestations of PCFCL, including macular erythematous/telangiectatic patches [3–5] or alopecic patches [6], have rarely been described and may pose a clinical diagnostic challenge for clinicians. Macular erythematous patches in well-established PCMZL cases have not been described to date in the literature [7, 8]. The aims of the present study were: (1) to extend the published experience with macular PCFCL; (2) to report cases of macular PCMZL; and (3) to correlate between the clinical and histopathological findings of patients with low-grade PCBCL presenting with erythematous-macules and to suggest a clinicopathological model for tumor progression of this lymphoma.

**Patients and Methods**

**Study Cohort and Setting**

The cohort included 14 patients with PCBCL manifesting with erythematous macules, at presentation or during the disease course, with/without the typical infiltrated plaques and nodules/tumors of PCBCL. All were diagnosed and managed at the cutaneous lymphoma clinics of two tertiary medical centers (Sheba, or Rabin Medical Centers, Israel), between January 2000 and December 2019. The diagnosis of PCFCL was based on the criteria of the WHO-EORTC classification [1]. Data on clinical history, description of the rash, laboratory, imaging results, treatment, and follow-up were retrospectively retrieved from the medical files. Cases in which the clinical description of the rash was ambiguous were excluded. The study was approved by the local ethics committees.

**Clinical Evaluation**

General work-up included complete blood count, serum chemistry (including lactic dehydrogenase), β-2 microglobulin, serology for *Borrelia burgdorferi* in cases of PCMZL, positron emission tomography computed tomography in all cases, and bone marrow biopsy in patients with follicle center lymphoma (FCL) and a few with marginal zone lymphoma (MZL). Staging was conducted according to the International Society for Cutaneous Lymphomas-EORTC staging classification for PCLs other than mycosis fungoides (MF) and Sézary syndrome [9], and specifically according to the recommendations for the management of cutaneous B-cell lymphomas [10].

**Histopathological, Immunohistochemical, and Genotypic Evaluation**

Biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, and 4 µm sections were stained with hematoxylin and eosin for histopathological evaluation. Immunophenotype assessment was performed with a panel of antibodies, including: CD3, CD20, CD10, CD21, BcL-2, BcL-6, Ki67, kappa, and lambda light chains. LN-1 and LN-2 were conducted on the oldest biopsies as a marker of B-cell tumor, as previously reported [11]. Whenever available, the polymerase chain reaction (PCR) analyses of the immunoglobulin heavy chain (IgH) were performed, as previously described [12, 13]. For the present study, biopsy specimens of both the macules and the typical nodules, if present, were reviewed by two pathologists (A.B. and E.D.). In addition to the final diagnosis, both pathologists classified the pattern of the infiltrate at scanning magnification as perivascular, interstitial, micronodular, nodular, and diffuse. Micronodules, a vague term for lymphocytic infiltrate of the skin, were defined following Giulia et al. [14], as relatively small aggregates of lymphocytes with morphological features seen in either FCL or MZL, without the formation of clear-cut lymph follicles, and by immunophenotype of B cells comprising at least 25% of the lymphocytes in these aggregates. Both pathologists had to agree on its presence in order to be included in the pattern analysis.

**Results**

The final diagnosis was made after integrating the clinical, histopathological, immunophenotypic, and genotypic findings. Eight patients were diagnosed with PCFCL and 6 with PCMZL (Table 1).

**Clinical Findings**

The vast majority were male patients (12 male and 2 female), aged 16–67 years at diagnosis. All 14 patients had erythematous nonscaly well or ill-defined patches, measuring 1–15 cm, some showing figurate or reticular configurations (Fig. 1a), with delicate follicular accentuation observed in half (Fig. 1b, c). In 3 patients (nos. 1, 3, 5), the macules were the presenting lesions, and in 2 patients (nos. 1, 5), they were the only manifestation of PCBCL during a follow-up period of 7 and 14 years, respectively. In the remaining 12 patients, infiltrated plaques, nodules/tumors developed either before, concomitantly with, or after the appearance of the macular lesions. Predilection of macular lesions was usually in accordance to the classic localization of each type of these low-grade PCBCLs: PCFCL preferentially involved the head (5 of 8 patients) usually as solitary or grouped regional lesions, while PCMZL involved preferentially the limbs (5 of 6 patients), usually as generalized multifocal disease. The initial clinical differential diagnosis included unusual PCBCL, a vascular lesion (particularly angiosarcoma), intravascul-
### Table 1. Patients with macular type of primary cutaneous B-cell lymphoma: clinical and histopathological data

| Patient No./age (years), gender | T stage/distribution | Clinical findings/presence of typical lesions of cutaneous B-cell lymphoma (yes/no) | Histopathological and genotypic findings of a macular lesion | dermal infiltrate pattern | immunostaining: CD20/CD3 (%) | PCR of IgH |
|--------------------------------|----------------------|---------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------|-------------------------------|--------------|
| **Follicle center-cell lymphoma** |                      |                                                                                 |                                                          |                          |                               |              |
| 1/64, male                      | T2b/regional         | Erythematous patches on the abdomen, at presentation/no                          | Superficial and deep, perivasculav, with micronodular formation | 60/40                    | LN-1+, LN-2+, BCL2– in B cells BCL2+ in T cells | Ki-67: 10%  | Monoclonal                   |
| 2/57, male                      | T1b/solitary         | Erythematous patch on the forehead/yes                                           | Superficial and deep perivasculav and interstitial, periadnexal, with micronodular formation | 60/40                    | BCL6+, CD10 partial+, BCL2– in B cells BCL2+ in T cells | Ki-67: 20%  | Monoclonal                   |
| 3/50, male                      | T3a/generalized      | Erythematous patches with some follicular accentuation on the upper and lower limbs, at presentation/yes | Superficial and deep perivasculav, and periadnexal, including peri-infundibular | 50/50                    | BCL6+, CD10-BCL2– in B cells BCL2+ in T cells | Ki-67–25%  | Monoclonal                   |
| 4/67, male                      | T2c/regional         | Erythematous patches on the scalp, forehead, and cheeks with some follicular accentuation/yes | Superficial and deep perivasculav, periadnexal, and specifically peri-infundibular with micronodular/ nodular formation | 40/60                    | BCL6+, CD10-BCL2– in B cells BCL2+ in T cells | Kappa/lambda light chains – polytypic | Not done* |
| 5/52, male                      | T1a/solitary         | Erythematous patch on the scalp, at presentation/no                             | Superficial and deep perivasculav, and periadnexal, with micronodular/ nodular formation | 50/50                    | BCL6+, CD10-BCL2– in B cells BCL2+ in T cells | Kappa/lambda light chains – polytypic | Polyclonal |
| 6/66, male                      | T1a/solitary         | Erythematous patch with some follicular accentuation on the scalp/yes            | Superficial and deep perivasculav, and specifically peri-infundibular with micronodular formation | 30/70                    | BCL6+, CD10-BCL2– in B cells BCL2+ in T cells | Kappa/lambda light chains – polytypic | Polyclonal* |
| 7/36, male                      | T1b/solitary         | Erythematous patch on the forehead with follicular accentuation/yes             | Superficial and deep perivasculav, interstitial, and periadnexal, specifically peri-infundibular with micronodular/ nodular formation | 50/50                    | BCL6+, BCL2– in B cells BCL2+ in T cells | Kappa/lambda light chains – polytypic | Polyclonal |
| 8/43, male                      | T3a/generalized      | Erythematous patch on the chest, and upper limbs, with follicular accentuation on the arm/yes | Superficial and deep perivasculav and periadnexal | 50/50                    |                                |              | Monoclonal                   |
| **Marginal zone lymphoma**      |                      |                                                                                 |                                                          |                          |                               |              |
| 9/66, male                      | T3a/generalized      | Erythematous patches on the limbs/yes                                           | Superficial and deep perivasculav, and periadnexal, with micronodular/ nodular formation | 60/40                    | BCL2+ in both B and T cells. Kappa light chain: monotypic | Not done* |
| 10/33, female                   | T3b/generalized      | Erythematous patches on the back and arms/yes                                   | Superficial and deep perivasculav, and periadnexal, with micronodular formation | 60/40                    | BCL2+ in both B and T cells CD10-Kappa light chain: monotypic | Polyclonal |
| 11/16, male                     | T3b/generalized      | Erythematous patches on the lower limbs with follicular accentuation/yes        | Superficial and deep, perivasculav, interstitial, and periadnexal | 20/80                    | BCL2+ in both B and T cells BCL6-CD10-Kappa light chain: monotypic | Polyclonal |
| 12/25, female                   | T1b/solitary         | Erythematous patch with follicular accentuation on a lower limb/yes             | Superficial and deep perivasculav, and periadnexal, with micronodular formation | 50/50                    | CD10-Ki-67: 30% Kappa light chain: monotypic | Not done |
| 13/41, male                     | T3a/generalized      | Erythematous patches on the upper and lower limbs/yes                           | Superficial and deep, perivasculav, and periadnexal, with micronodular/ nodular formation | 30/70                    | BCL2+ in both B and T cells CD138+, many plasma cells Kappa light chain: monotypic | Monoclonal |
| 14/55, male                     | T1a/solitary         | Erythematous patch on the back/yes                                             | Superficial and deep, perivasculav, interstitial, and periadnexal, with micronodular formation | 40/60                    | BCL2+ in both B and T cells Kappa light chain: monotypic | Monoclonal |

PCR, polymerase chain reaction; IgH, immunoglobulin heavy chain. * Monoclonal in typical nodular lesion in this patient.
Macular Type of Primary Cutaneous B-Cell Lymphoma

**Histological, Immunohistochemical, and Genotypic Findings**

Biopsy specimens obtained from the macular erythematous lesions in all 14 cases showed a distinct dermal pattern of superficial and deep lymphocytic perivascular infiltrate, with an occasional interstitial component and a peri-adnexal lymphocytic infiltrate (with dense peri-infundibular infiltrates in 4 patients). Micronodule formation was observed in all but 3 patients (nos. 3, 8, 11). Nodule formation was observed in only 4 of the 11 cases with micronodules. Mucin deposition was not observed in any of the biopsies. In all cases, most of the lymphocytes were small, and the B-cell cytology was in accordance with the final diagnosis.

Phenotypically, B cells comprised the majority of the lymphocytes in only 4 patients, and even then, they accounted for only 60% of the lymphocytic population. In the remaining 10 patients, B and T cells were either equally distributed, or T cells outnumbered B cells (nos. 4, 6, 11, 13, 14). Further immunohistochemical (CD10, BCL6, CD21, BCL2, kappa and lambda chains, and Ki67) analysis showed characteristic findings of either FCL or MZL (Table 1). Specifically, irregular follicular dendritic cells (FDC) network, representing follicular growth pattern, was present in all cases but one (no. 8) of PCFCL. Disrupted FDC network was present also in 4 cases (nos. 9–12) of PCMZL, but this was in the context of reactive germinal centers with follicular colonization.

PCR analyses of the IgH gene rearrangement performed on a biopsy obtained from a patch, conducted on 11 patients, showed a monoclonal rearrangement in 7. Examples of the histopathological findings of FCL are shown in online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000525439), and of MZL in online supplementary Figure S2. In 7 patients, the final histopathological diagnosis of FCL or MZL was made based on the histopathological and immunohistochemical findings, with either molecular studies not done or showing polyclonality for IgH (Table 1).

In the 5 cases with T-cell predominance, typical lesions of PCBCL were also present, and the final diagnosis of the macular lesion was rendered with certainty only after integrating the clinical, pathological, and molecular findings. Specifically, in patient no. 6, a diagnosis of early FCL was rendered despite CD20 staining in about 30% of the cells, because CD21 staining showed FDC network, pointing to a follicular growth pattern, and the patient had already been diagnosed with unequivocal PCFCL clinically, histologically, and by IgH monoclonality, rendered from a typical nodular lesion.

In the 3 patients without micronodule formation (nos. 3, 8, 11), the histopathological findings were difficult to interpret and read as atypical lymphoid infiltrate. In one case (no. 3, initial clinical and histopathological features are shown in online suppl. Fig. S3A–D), the diagnosis was made only after 5 years, when small papules appeared, showing nodular infiltrate of mono-

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**Fig. 1.** Clinical presentations of macular low-grade primary cutaneous B-cell lymphoma. **a** Ill-defined reticulate, net-like, erythematous patches on the outer aspect of the arm (PCMZL, patient 10). **b** Erythematous patch on the forehead and the adjacent scalp with follicular accentuation. Note the adjacent typical nodular lesion (PCFCL, patient 7). **c** Erythematous patches, in some with follicular accentuation on the limb (PCMZL, patient 11).
clonal B cells (online suppl. Fig. S3A, E–G). In the other 2 cases (nos. 8 and 11), the diagnosis was based on the past history of well-established classic PCBCL, combined with the immunophenotypic findings and/or IgH monoclonality of the macular lesions which was identical to that in the nodules. Biopsies obtained from the typical plaques/nodules in 12 patients showed the classic pathological features of either MZL or FCL, that is, nodular and/or diffuse dermal lymphoid infiltrate of the B cell of origin [1].

Treatment and Follow-Up
Treatment consisted of the common modalities used for low-grade PCBCL, including potent topical steroids, localized radiation courses, systemic rituximab, or watch-and-wait strategy. The median duration of follow-up was 7 years (mean 6 years, range 0.5–14). At the last follow-up visit, all patients were alive without evidence of extracutaneous spread: 7 had no evidence of disease and 7 had minimal disease. Of note, in 2 patients (nos. 11, 12), Hodgkin lymphoma was diagnosed 2 years after the diagnosis of their skin lymphoma.

Discussion
We describe a series of 14 patients with low-grade PCBCL who presented with erythematous macules. This report extends the few published reports on PCFCL presenting as macular lesions and in addition describes a series of PCMZL, not hitherto reported. In 12 of our 14 patients, typical papulonodular/tumoral lesions of PCBCL were observed at a certain stage, whereas in 2 patients, macular lesions were the only presentation.

Massone et al. [3] described 13 patients with cutaneous FCL that manifested only as large macules on the head at presentation: 11/13 patients had PCL. de Masson et al. [6] recently reported 14 cases with PCFCL presenting with isolated or multiple alopecic patches on the scalp, some with telangiectasia. In contrast, in the present series of PCFCL, in the vast majority of such cases (6/8), macular lesions were not the sole manifestation of the lymphoma, and cases located in areas other than the head were identified.

Perhaps, if longer follow-up had been conducted in previous reports (which was relatively short compared...
to the present cohort; median of 21.5 months [3] and 4.5 years [6], vs. 7 years), classic lesions of low-grade PCBCL including infiltrated plaques/nodules/tumors would have appeared. The distribution of the macular lesions in our 6 patients diagnosed with PCMZL was as expected in this type of PCBCL (mostly on the limbs and trunk).

According to the previous reports [3, 6] and the present cohort, macular lesions as a manifestation of low-grade PCBCL have a wide differential diagnosis, including mainly: erysipelas, rosacea, lupus erythematosus, sarcoidosis, macular amyloidosis, alopecia, figurate erythema, interstitial granuloma annulare, livedo reticularis, and drug eruption, and also of neoplastic process, such as vascular lesion (angiosarcoma), Kaposi sarcoma, intra-vascular lymphoma, and MF. Our cohort, together with the few previous cases with macular PCFCL [3–6], expands the list of the unusual manifestations of low-grade PCBCL [15].

A biopsy is indicated not only when macules are the first/sole manifestation of cutaneous B-cell lymphoma, but also in cases where there are coexisting typical lesions of PCBCL, in order to evaluate the extent of disease. It is not unlikely that macular lesions in such patients with classic lesions are underdiagnosed due to lack of awareness of this manifestation of the lymphoma.

Histopathologically, most cases in this cohort lacked nodule formations, which are typical for PCBCL, but rather showed superficial and deep perivascular with/without periadnexal infiltrate, or interstitial involvement (4 patients), usually with the formation of micronodules (11/14). Classic nodular or diffuse lymphoid infiltrates were observed in a minority of the cases (4/14). Of note, in all cases with nodules formation, micronodules were also present. Unlike the histological pattern in our cohort, Massone et al. described 11 patients with PCFCL, all with macules located predominantly on the scalp and forehead, with histological examination revealing follicular pattern of growth extending within the entire dermis and superficial part of the subcutaneous fat. de Masson et al. [6] in 14 cases of PCFCL of the scalp, presenting as scarring alopecia, reported histology of follicular/diffuse or mixed architecture [3]. We describe a new clinicopathological presentation of macular PCFCL or PCMZL, presenting with only superficial and deep perivascular with/without periadnexal infiltrate, or interstitial involvement alone, with no heavier nodular or diffuse pattern, which may be the earliest level in a spectrum, with a possible continuum of the clinical and pathological evolution of PCBCL.

Gulia et al. [14] described 24 patients with early PCFCL, clinically with multiple papules, termed diffuse type, with histological findings of superficial and deep perivascular and periadnexal lymphoid aggregates with a micronodular pattern but no clear-cut lymphoid follicle. This pattern is not dissimilar to the pattern observed in our patients, namely superficial and deep perivascular with/without periadnexal lymphoid infiltrate and with micronodule formation in most cases.

This morphological continuum from perivascular/periadnexal infiltrates to micronodules and nodules formation, and to the diffuse pattern [1, 3, 6] is well correlated with the immunophenotype and molecular findings: we observed a relatively low number of B cells, which, in general, correlated with the clinical appearance of the macules. Furthermore, the dendritic network was only partially lost in the micronodules. Taken together, the lesions described in our series represent clinically and histologically early PCBCL, shedding light on the morphological development of the disease, as suggested in Figure 2. This may also account for the monoclonality for IgH found only in about 60% of the cases tested, in analogy to early patch-stage MF, in which 50–60% of lesions analyzed by BIOMED-2 PCR assays demonstrate clonal rearrangement of the T-cell receptor [16, 17]. These findings, along with the number of micronodules and their size, may account for the fact that all the lesions described by Gulia et al. [14] were small papules, whereas the lesions in our patients were macules. However, the lack of clinicopathological correlation in 4 cases in the present cohort with nodular relatively heavy pattern on histology (2 with macules on the scalp, and 2 on the limbs), together with the previous cases of Massone et al. [3] and de Masson et al. [6], showing follicular/diffuse pattern of growth with clinical presentation of macules or scarring alopecia, and not with nodules or tumors, cannot be solely explained by the scalp being a “special site” of involvement, as 2 patients in the present cohort had lesions located on the limbs. This finding requires larger studies of macular lesions and further investigation.

Another clinical-pathological correlation that emerged from our series is the existence of a clinically “follicular” variant of PCBCL, consisting of hair-follicle-centered accentuation, or papules on the erythematous macule, on the forehead/limbs (Table 1; Fig. 1b, c), somewhat similar to those of early-stage folliculotrophic MF [18]. The histology of some of these cases revealed dense superficial perifollicular lymphocytic infiltrate, without follicular mucinosis (online suppl. Fig. S1E, F), which may account...
for the clinical finding. Garrido et al. [19] described a patient who presented with follicular papules, which on histology proved to be PCFCL in association with follicular mucinosis. Moreover, a recent report by Chockaligam et al. [20] described a case of PCFCL presenting as folliculitis. These 2 case reports along with the 14 cases of PCFCL presenting as isolated or multiple alopecic patches of the scalp [6] and the cases in the present study emphasize the existence of a “follicular” variant of PCBCL clinically and histologically. One patient in our cohort presented with ill-defined reticular, net-like, erythematous patches, somewhat resembling livedo reticularis (Fig. 1a). Cases of cutaneous B-cell lymphoma presenting with a “livedo” were rarely reported, mainly as livedo racemosa in intravascular lymphoma [21].

The course of the disease in our cohort was as expected for low-grade PCBCL, and the prognosis was excellent. Yet, these lesions may pose a therapeutic quandary. The combination of the course with occasional spontaneous remission and prognosis of these lymphomas in general, with the subtle presentation of these lesions in particular, supports a nonaggressive therapeutic approach such as watchful waiting and application of potent topical steroids as needed. However, if the goal is definitive complete remission, localized radiation is the treatment of choice.

This study was limited by the retrospective design, small sample, and limited follow-up data. Moreover, the term micronodule is not objectively defined for lymphocytic infiltrates in general and for the skin in particular, and thus, some overlap between dense perivascular/perivascular and interstitial infiltrate and micronodules may exist on one hand and between micronodule and nodule on the other hand. However, it is our opinion that the experienced dermatopathologist can recognize these patterns. Furthermore, the presence of some overlap emphasizes that a clinical pathological “progression” model for PCBCL may exist.

To conclude, the current series further expands the clinical and histological spectrum of the macular form of PCBCL. Similar to many skin diseases, either inflammatory or neoplastic, there is an early phase in PCBCL, which has unique clinical-pathological characteristics.

This clinicopathological variant of the disease requires at times repeated biopsies and integration of the clinical, histological, and molecular findings to arrive at the right diagnosis. The study should alert dermatologists and pathologists to this macular, noninfiltrated presentation of low-grade PCBCL, which can pose clinical and sometimes also histopathological diagnostic difficulties.

Key Message

Low-grade primary cutaneous B-cell lymphoma may present with macular lesions, which can pose clinicopathological diagnostic difficulties.

Statement of Ethics

This study protocol was reviewed and approved by the IRB committee or Rabin Medical Center (approval number 5111) and by the IRB committee or Sheba Medical Center (approval number 5503-08-SMC). Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Aviv Barzilai, Iris Amitay-Laish, and Emmilia Hodak: substantial contributions to the conception or design of the work, acquisition, analysis, and interpretation of data for the work, drafting the work, and revising it critically, and moreover, final approval of the version to be published. Elena Didkovsky, Meora Feinmesser, Adam Dalal, and Ginette Schiby: acquisition, analysis, and interpretation of data for the work, drafting the work, and revising it, and moreover, final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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