Primary cutaneous T-cell lymphomas in childhood and adolescence

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Section Editor
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Summary
Primary cutaneous lymphomas are extranodal non-Hodgkin lymphomas of T- or B-cell origin, that predominantly affect older patients but have been reported in all age groups and as early as in the first years of life. Diagnosis of cutaneous lymphomas is challenging and requires high clinical suspicion and close collaboration between dermatologists, pediatric oncologists and pathologists. Skin involvement of non-Hodgkin lymphomas in children or adolescents can either be primary cutaneous or secondary due to an underlying nodal lymphoma. The most common primary cutaneous lymphomas encountered in children are of T-cell origin, with mycosis fungoides being the most prevalent cutaneous T-cell lymphoma, followed by CD30+ lymphoproliferative disorders. While cutaneous lymphomas share clinicopathologic characteristics between juvenile and adult forms, there are important differences in terms of clinical presentation, diagnosis and treatment. The hypopigmented variant of mycosis fungoides seems to be overrepresented in the pediatric age group. Prognosis and treatment of mycosis fungoides are stage dependent. The majority of children present with early-stage disease and respond well to topical corticosteroids and phototherapy.

Overview
Primary cutaneous lymphomas (PCL) are by definition limited to the skin without any evidence of extracutaneous disease at the time of diagnosis [1, 2]. PCL is a broad term for a heterogenous group of cutaneous lymphomas of T- (CTCL) and B-cell (CBCL) origin [1]. They are the second most common group of extranodal non-Hodgkin lymphomas and should always be distinguished from systemic lymphomas affecting the skin secondarily [1]. CTCL account for 75–80 % of all PCL, whereas CBCL account for 20–25 % [2]. PCL differ not only in their cells of origin, but also in their clinical behavior, histopathologic and molecular presentation as well as treatment and prognosis [2].

Primary cutaneous lymphomas usually affect patients in later decades of life, but can also arise in children and adolescents. The most common PCL seen in childhood are mycosis fungoides (MF) and CD30+ lymphoproliferative disorders.
Mycosis fungoides

Epidemiology and clinical presentation

Mycosis fungoides represents the most common form of PCL both in adults and children with an estimated age-adjusted incidence rate of 4.1 per 1,000,000 person-years (age-adjusted to the 2000 US standard population) [4, 7]. The prevalence of juvenile MF varies geographically and accounts for approximately 5 % of all MF cases in US- and European studies and up to 17 % in an Arabic cohort [8, 9].

Over the last years more than 300 cases of juvenile-onset MF have been published by researchers from dedicated cutaneous lymphoma clinics around the globe (Table 1) [6, 8, 10–17, 18–24]. These reports provide important information on the clinical and histopathological presentation, treatment and prognosis of childhood MF.

The mean age at diagnosis for juvenile MF is 11.0 years. MF is more commonly diagnosed in boys than in girls, with a ratio of 1.4:1 (Table 1). MF is staged according to the International Society for Cutaneous Lymphomas (ISCL) and European Organization for Research and Treatment of Cancer (EORTC) classification of MF and SS (Tables 2, 3) [25].

Juvenile MF is diagnosed in early disease stages in more than 95 % (Table 1) of children with either limited patches or plaques involving < 10 % body surface area (BSA) (IA) or generalized patches/plaques > 10 % BSA (IB). However children with advanced disease stages and disease progression leading to a fatal outcome have been reported as well [10, 16].

MF has many faces and often resembles benign inflammatory skin diseases [26], thus resulting in a median diagnostic delay of three years [27]. A large single center study of childhood MF published by Heng and coworkers found that only 41.3 % of all patients were diagnosed before skin biopsy [23]. Knowledge of the different clinical presentations of juvenile MF may help to differentiate the disease from benign inflammatory or autoimmune diseases (Figure 1) [26].

While most adult MF patients present with erythematous patches or plaques on sun protected areas of the body, most pediatric MF patients don’t have a classic presentation [9]. The majority of children with MF present with atypical variants, with hypopigmented MF being the most prevalent from, seen in over 60 % of all juvenile cases (Table 1) [8, 22, 23]. This MF variant seems to be overrepresented in young patients, compared to older patients who it accounts for less than 10 % of all MF variants and is generally more prevalent in skin of color [22]. Other forms include hyperpigmented MF, folliculotroping MF (FMF), poikilodermatous MF, unilesional MF and overlapping variants with a combination of features (e.g., hypo- and hyperpigmented patches, hypopigmented and erythematous patches and plaques) [8, 17, 21, 22].

Despite the vast variety of MF presentations, only FMF, Pagetoid reticulosis and granulomatous slack skin (GSS) are recognized as different disease variants by the current EORTC-WHO classification for PCL, due to their different clinical and pathophysiological behavior [2].

Hypopigmented MF

Children and adolescents with this MF variant have hypopigmented patches or plaques. Hypopigmented MF has been the most prevalent form of pediatric MF encountered in the review performed (Table 1). Differential diagnoses include vitiligo, postinflammatory hypopigmentation and pityriasis alba (Figure 1). Castano et al. studied 35 cases of pediatric hypopigmented MF and found that up to three
Table 1  Summary of mycosis fungoides studies in children and adolescents.

| Study             | n   | Gender | Age | Stage | Clinical presentation | Treatment                                      | Status at last follow-up            |
|-------------------|-----|--------|-----|-------|-----------------------|------------------------------------------------|--------------------------------------|
| Peters et al.     | 5   | M:60%  | 14  | Not reported | Not reported           | – Topical nitrogen mustard (80%)                | – Died of Hodgkin disease (40%)     |
| 1990/USA [16]     |     | F:40%  |     |       |                       | – Local radiation (40%)                         | – Stable disease (20%)              |
|                   |     |        |     |       |                       | – PUVA (20%)                                    | – Not reported (40%)                |
| Hickham et al.    | 5   | M:60%  | 15.2| IA (20%) | Not reported           | – Topical nitrogen mustard (80%)                | – Died of disease (40%)             |
| 1997/USA [10]     |     | F:40%  |     | IIA (60%) |                       | – Stable disease (20%)                          | – Lost to follow–up (20%)           |
|                   |     |        |     | IIB (20%) |                       | – Interferon–alpha (40%)                        | – Complete remission (20%)          |
|                   |     |        |     |       |                       |                                                  |                                      |
| Pabsch et al.     | 5   | M:60%  | 11.6| I (100%) | Classic MF (60%)      | – PUVA (60%)                                    | – Complete remission (100%)         |
| 2002/Germany [11] |     | F:40%  |     |       |                       | – Topical corticosteroids only (40%)            |                                      |
| Boccara et al.    | 5   | M:80%  |     | –     | CD8+ MF                | – Not reported                                  | – Complete remission (80%)          |
| 2012/France [6]   |     | F:20%  |     |       |                       | – Complete remission (20%)                      |                                      |
|                   |     |        |     |       | Hypopigmented MF      | – CD8+ MF (100%)                                |                                      |
|                   |     |        |     |       | Transformed MF        | – PUVA (33%)                                    |                                      |
|                   |     |        |     |       | Granulomatous Slack Skin (4 patients combined with PLC) | – Local radiation (17%) | – Partial remission (33%) | – Stable disease (33%) | – Lost to follow–up (17%) |
| Whittam et al.    | 6   | M:17%  | 13.2| IA (50%) | CD8+ MF (100%)        | – Topical corticosteroids only (40%)            |                                      |
| 2000/UK [12]      |     | F:83%  |     | IB (50%) |                       | – Complete remission (17%)                      |                                      |
|                   |     |        |     |       |                       |                                                  |                                      |
| Koh et al. 2014/  | 9   | M:89%  | 8.8 | IA (22%) | Hypopigmented MF (100%) | – NB–UVB (100%)                                 | – Complete remission (44%)          |
| Singapore [13]    |     | F:11%  |     | IB (67%) | combined with PLC (56%) |                                                | – Stable disease (33%)             |
|                   |     |        |     | IIA (11%) |                       | – Lost to follow–up (22%)                       |                                      |
| Cervini et al.    | 14  | M:43%  | 11.4| IA (14%) | Hypopigmented MF (100%) | – Progressive disease (29%)                     | – Stable disease (36%)             |
| 2017/Argentina [14]|     | F:57%  |     | IB (79%) | combined with classic MF (43%) | – Complete response (29%) | – Complete response (29%) | – Stable disease (36%) |
|                   |     |        |     | IV (7%) |                       | – Lost to follow–up (7%)                        |                                      |
| Study                        | n   | Gender       | Age | Stage       | Clinical presentation                                                                 | Treatment                                                                 | Status at last follow-up                      |
|-----------------------------|-----|--------------|-----|-------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------|
| Yazganoglu et al. 2013/Turkey | 20  | M: 60 % (12/20) F: 40 % (8/20) | 9.2 | IA (60 %)   | Hypopigmented MF (45 %), combined with classic MF (30 %)                              | NB–UVB (30 %)                                                             | No recurrence (20 %)                          |
|                             |     |              |     | IB (40 %)   |                                         | PUVA (15 %)                                                              | Complete response (15 %)                       |
|                             |     |              |     |             |                                         | Topical corticosteroids only (45 %)                                      | Recurrence (40 %)                            |
|                             |     |              |     |             |                                         | Topical bexarotene (5 %)                                                 | No resolution (10 %)                          |
|                             |     |              |     |             |                                         | Topical carmustine (5 %)                                                  | Under treatment at last follow–up (15 %)      |
| Kim et al. 2009/Korea       | 21* | M: 76 % (16/21) F: 24 % (5/21) | 10  | IA (52 %)   | Hypopigmented MF (29 %)                                                              | NB–UVB (14 %)                                                             | Complete response (10 %)                      |
|                             |     |              |     | IB (48 %)   | Classic MF (14 %)                                                                      | PUVA (81 %)                                                              | Partial response (90 %)                       |
|                             |     |              |     |             | MF variants (57 %)                                                                    | Topical calcipotriol (19 %)                                               |                                              |
| Ocampo et al. 2020/Colombia | 23  | M: 57 % (13/23) F: 43 % (10/23) | 12.4| IA (26 %)   | Hypopigmented MF (52 %)                                                              | NB–UVB (52 %)                                                             | Complete response (35 %)                      |
|                             |     |              |     | IB (74 %)   | Classic MF (30 %)                                                                      | PUVA/Bath PUVA/UV–1A (78 %)                                               | Partial response (9 %)                        |
|                             |     |              |     |             | Foliculotrophic MF (17 %)                                                            |                                                                            | Active disease (22 %)                         |
| Laws et al. 2014/Canada     | 28  | M: 46 % (13/28) F: 54 % (15/28) | 11.6| IA (36 %)   | Hypopigmented MF (79 %)                                                              | NB–UVB (64 %)                                                             | Complete response (36 %)                      |
|                             |     |              |     | IB (61 %)   | Classic MF (21 %)                                                                      | Bath PUVA (29 %)                                                          | Partial response (36 %)                       |
|                             |     |              |     |             | not staged (4 %)                                                                       | TSEB (7 %)                                                               | Stable disease (11 %)                         |
|                             |     |              |     |             |                                                                            | Retinoids (19 %)                                                         | Under treatment (11 %)                        |
|                             |     |              |     |             |                                                                            | Topical imiquimod (11 %)                                                  | No Information (7 %)                          |
| Nasimi et al. 2019/Iran     | 30  | M: 57 % (17/30) F: 43 % (13/30) | 10.9| IA & IB (97 %) | Hypopigmented MF (57 %)                                                              | NB–UVB (100 %)                                                            | Complete or partial response (57 %)          |
|                             |     |              |     | IIB (3 %)   | Classic MF (20 %)                                                                      |                                                                            | No response (43 %)                            |
| Boulos et al. 2014/USA      | 31* | M: 55 % (17/31) F: 45 % (14/31) | 13.4| IA (45 %)   | Hypopigmented MF (35 %)                                                              | NB–UVB/UVB (68 %)                                                         | Complete response (23 %)                      |
|                             |     |              |     | IB (52 %)   | Hyperpigmented MF (13 %)                                                             | PUVA (10 %)                                                              | Partial response (39 %)                       |
|                             |     |              |     |             | Hypo/hyperpigmented MF (16 %)                                                       | Topical nitrogen mustard (13 %)                                           | Stable disease (16 %)                         |
|                             |     |              |     |             | Classic MF (26 %)                                                                     | Interferon (13 %)                                                        | Progressive disease (6 %)                     |
|                             |     |              |     |             | Granulomatous Slack Skin (3 %)                                                        | TSEB/local radiation (6 %)                                                | Not reported (16 %)                           |
|                             |     |              |     |             | Foliculotrophic MF (3 %)                                                             | Retinoids oral (6 %)                                                     |                                              |
|                             |     |              |     |             | Poikiloderma (3 %)                                                                   | Retinoids topical (16 %)                                                 |                                              |
| Castano et al. 2013/USA     | 32* | M: 59 % (19/32) F: 41 % (13/32) | 11.9|             | Hypopigmented MF (94 %)                                                              | NB–UVB/UVB (72 %)                                                         | Complete response (16 %)                      |
|                             |     |              |     |             | Hyperpigmented MF (6 %)                                                               | PUVA (3 %)                                                               | Partial response (11 %)                       |
|                             |     |              |     |             |                                                                            | Topical corticosteroids (31 %)                                            | Progressive disease/active disease (31 %)     |
|                             |     |              |     |             |                                                                            | Recurrence (16 %)                                                        |                                              |
|                             |     |              |     |             |                                                                            | Lost to follow–up (25 %)                                                 |                                              |
| Study                  | n   | Gender     | Age | Stage          | Clinical presentation                                                                 | Treatment                     | Status at last follow-up |
|-----------------------|-----|------------|-----|----------------|---------------------------------------------------------------------------------------|-------------------------------|--------------------------|
| Nanda et al. 2010/Kuwait [8] | 36  | M: 56 % (20/36) F: 44 % (16/36) | 12.9 | IA (17 %)      | - Hypopigmented MF (56 %)                                                            | - Not reported                | - Not reported           |
|                       |     |            |     | IB (75 %)      | - Hyperpigmented MF alone (11 %) and combined with PLC (3 %)                          |                               |                          |
|                       |     |            |     | IIA (8 %)      | - Classic MF (14 %)                                                                   |                               |                          |
|                       |     |            |     |                | - Unilesional (6 %)                                                                   |                               |                          |
|                       |     |            |     |                | - PLC alone (3 %)                                                                    |                               |                          |
| Heng et al. 2014/Singapore [23] | 46  | M: 70 % (32/46) F: 30 % (14/46) | 10.3 | IA (39 %)      | - Hypopigmented MF (91 %)                                                            | - NB–UVB (47 %)               | - Complete response (30 %) |
|                       |     |            |     | IB (59 %)      | - PLC–like MF (2 %)                                                                  | - PUVA/UVA (9 %)              | - Partial response (9 %)  |
|                       |     |            |     | IIA (2 %)      | - PPD–like MF (2 %)                                                                  | - Topical corticosteroids alone (17 %) | - No improvement (2 %)  |
|                       |     |            |     |                | - Classical MF (2 %)                                                                  |                               | - Recurrence (7 %)       |
|                       |     |            |     |                | - Solitary MF (2 %)                                                                  |                               | - Lost to follow–up (52 %) |
| Hodak et al. 2014/Israel [24] | 50  | M: 60 % (30/50) F: 40 % (20/50) | 7.4  | IA (52 %)      | - Hypopigmented (58 %)                                                               | - NB–UVB/BB–UVB (32 %)        | Patients with non–FMF (n = 32) |
|                       |     |            |     | IB (37 %)      | - FMF (36 %)                                                                        | - PUVA (18 %)                 | - Complete response (59 %) |
|                       |     |            |     | IIA (6 %)      | - Psoriasiform (20 %)                                                                | - Topical nitrogen mustard    | - Active disease (38 %)  |
|                       |     |            |     | IIB (2 %)      | - Classic MF (16 %)                                                                  | (4 %)                         | - Progressive disease (3 %) |
|                       |     |            |     |                | - Hyperpigmented MF (2 %)                                                            | - Surgical excision (2 %)      | Patient with FMF (n = 17) |
|                       |     |            |     |                | - Unilesional MF (6 %)                                                               | - Climatotherapy (4 %)        | - Complete response (59 %) |
|                       |     |            |     |                |                                                                                     |                               | - Active disease (35 %)  |
|                       |     |            |     |                |                                                                                     |                               | - Disease progression (6 %) |
| Total                 | 366 | M: 59 % (216/366) F: 41 % (150/366) | 11.0 | IA: 3.5 % (114/327) | - Hypopigmented MF: 63 % (224/356)                                                  | - NB–UVB/UVB: 56 % (176/319)   | n.a.                     |
|                       |     |            |     | IB: 50 % (164/327) | - Classic MF: 15 % (54/356)                                                          | - PUVA: 26 % (83/319)         | Outcome/treatment response |
|                       |     |            |     | I n.s.: 10 % 32/327 | - FMF: 6 % (23/356)                                                                  | - Topical corticosteroids: 15 % (47/319) | not uniformly reported. |
|                       |     |            |     | IIA: 3 % (11/327) | - Unilesional MF: 3 % (10/356)                                                       |                               |                          |
|                       |     |            |     | IIB: 0.9 % (3/327) | - CD8+ MF: 5 % (19/356)                                                              |                               |                          |
|                       |     |            |     | IV: 0.9 % (3/327) | - Other variants: 12 % (43/356)                                                      |                               |                          |
|                       |     |            |     |                |                                                                                     | - Retinoids: 6 % (8/319)       |                          |
|                       |     |            |     |                |                                                                                     | - Topical nitrogen mustard: 5 % (15/319) |                          |
|                       |     |            |     |                |                                                                                     | - TSEB/Local radiation: 3 %   |                          |
|                       |     |            |     |                |                                                                                     (10/319)                        |                          |
|                       |     |            |     |                |                                                                                     - Interferon–alpha: 3 %    |                          |
|                       |     |            |     |                |                                                                                     (8/319)                        |                          |
|                       |     |            |     |                |                                                                                     - SCT: 0.6 % (2/319)          |                          |

Abbr.: F, female; FMF, folliculotropic mycosis fungoides; M, male; MF, mycosis fungoides; n, number; n.a., not applicable; NB–UVB, narrow band ultraviolet light B; n.s. not specified; PLC, pityriasis lichenoides chronica; PPD, Pigmented purpuric dermatoses; PUVA, Psoralen plus ultraviolet light A; SCT, stem cell transplantation; UVB, ultraviolet light B.

*Kim et al. reported a total of 23 patients, 21 were 18 or younger at diagnosis and thus included in this table.

*Boulos et al. reported a total of 34 patients, 31 were 18 or younger at diagnosis and thus included in this table.

*Castano et al. reported a total of 35 patients, 32 were 18 years or younger at diagnosis and thus included in this table.
Children with hypopigmented MF patches and plaques tend to have darker skin types. Biopsies were needed to establish a correct diagnosis [22]. Children with hypopigmented MF patches and plaques tend to have darker skin types (Fitzpatrick IV–VI) [19, 20, 22, 23, 28], prompting the question whether this variant is truly more prevalent in skin of color or whether it is underdiagnosed in patients with fair skin. It is also possible to have hypopigmented lesions along with classic erythematous MF lesions [22]. This is important, because while most patients (both adults and children) with hypopigmented MF have an excellent prognosis, studies have shown that children with both hypopigmented and classic MF patch lesions may experience progressive disease to plaque and tumor stage MF [22, 28].
Biopsies from hypopigmented MF lesions show epidermotropism of small-to-medium-sized lymphocytes (comparably with classic MF patch lesions). Immunohistochemically, CD7 staining is reduced and the atypical lymphocytes are CD8⁺ compared to classic MF where the malignant cells are predominantly CD4⁺ [22].

Folliculotropic MF

Clinically, FMF presents with indurated patches and plaques often on hair bearing body parts including the face, eyebrows and scalp, along with acneiform lesions and alopecia [29–31]. In children, FMF features are often more subtle, compared to adult patients and present as grouped follicular papules and patches with associated hair loss on the trunk, arms and legs [24]. Differential diagnoses include pityriasis rubra pilaris, keratosis pilaris and alopecia mucinosa (Figure 1). Hodak et al. reported a large series of juvenile MF cases where FMF was the second most prevalent

Table 3 ISCL/EORTC clinical staging of mycosis fungoides and Sézary syndrome.

| Stage | T  | N  | M  | B     |
|-------|----|----|----|-------|
| IA    | 1  | 0  | 0  | 0, 1  |
| IB    | 2  | 0  | 0  | 0, 1  |
| IIA   | 1–2| 1–2| 0  | 0, 1  |
| IIB   | 3  | 0–2| 0  | 0, 1  |
| IIIA  | 4  | 0–2| 0  | 0     |
| IIIB  | 4  | 0–2| 0  | 1     |
| IVA   | 1–4| 0–2| 0  | 2     |
| IVA₂  | 1–4| 3  | 0  | 0–2   |
| IVB   | 1–4| 0–3| 1  | 0–2   |

ISCL/EORTC, International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer [25].

Figure 1 Differential diagnoses of important mycosis fungoides variants.
variant, accounting for 36% of all patients [24]. Interestingly, the majority of FMF cases in their cohort had a combination of hypopigmented and typical FMF lesions [24]. Histopathologically, FMF is characterized by neoplastic lymphocytes infiltrating the hair follicles [32]. The interfollicular epidermis is usually spared and Pautrier’s microabscesses are infrequently seen, in contrast to classic MF [33].

Due to the deep perifollicular infiltrates seen pathologically in FMF, this variant was previously thought to be an independent prognostic indicator for poor outcome. However, newer studies have shown that FMF patients can be subdivided into two clinical groups, an early indolent group of patients with follicle-based patches, flat plaques, keratosis pilaris like and acneiform lesions and an advanced stage group of patients having thick follicle-based infiltrated plaques and tumors. The latter group is less responsive to therapies and carries a worse prognosis [29–31, 34, 35].

The majority of children with FMF have early-stage disease and respond well to bath or systemic psoralen and ultraviolet A (PUVA) [31, 36].

The differentiation of FMF from primary follicular mucinosis is difficult and is subject of debate. Follicular mucinosis describes the presence of mucin deposits around hair follicles, a pathologic description that is often present in FMF biopsies [37, 38]. In adults, primary follicular mucinosis presents clinically with diffuse cutaneous lesions and is considered a variant of MF. In children, primary idiopathic follicular mucinosis commonly appears as localized patches with follicular papules often involving the head and neck and either resolves spontaneously or respond well to topical steroids or phototherapy. Prognosis is usually excellent [37].

**Pagetoid reticulosis**

Pagetoid reticulosis is rare, both in adults and in children. It is recognized as a different variant of MF by the EORTC-WHO classification for PCL [2]. Woringer and Kolopp reported the first case of Pagetoid reticulosis in 1939 in a 13-year-old boy. Since this original case, less than ten pediatric patients with pagetoid reticulosis have been published in the literature [4, 39–43]. Pagetoid reticulosis presents clinically as a solitary, erythematous slowly progressive plaque on the distal extremities (usually hands and feet). Histologically, a hyperplastic epidermis with epidermotropism and small to medium sized nests of pagetoid cells may be the evident finding [39]. Immunohistochemistry of the reported pediatric cases has shown a CD3+, CD4– and CD8+ phenotype [39–43]. Treatment modalities include surgery of the solitary lesions [41], radiotherapy [42, 43] and less common, photodynamic therapy [40]. The overall prognosis of pagetoid reticulosis is excellent and complete remissions have been achieved with the above-mentioned treatments.

**Granulomatous slack skin**

Granulomatous slack skin is a rare distinct disease variant of MF that is characterized by the presence of slowly developing pendulous bulky skin folds, located in the flexural areas [2]. Histologically large multinucleated giant cells (immunophenotypically expressing CD68) emperiplois and loss of elastic tissue are evident [44, 45]. Treatments among others include PUVA, radiotherapy, interferon alpha and surgery, but treatment outcomes are often disappointing [46]. It is important to note, that patients with GSS may also have or develop associated other malignant lymphomas. So far, only few cases of pediatric GSS have been reported in the literature [46, 47].
In 1997 Moreno-Giménez et al. described the case of an 11-year-old boy with GSS who was initially successfully treated with systemic corticosteroids and surgical excision of the localized bulky groin lesions [47]. Ten years later the same group published the follow-up data of their initial report. The child experienced several relapses over a course of ten years and died at the age of 20, despite treatment escalation with chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) [48].

Work-up and staging

Every child with a clinical suspicion for MF/Sézary-Syndrom (SS) should undergo a complete physical examination including the documentation of the extent of BSA and determination of the morphology of skin lesions (patch/plaques/tumors) [49]. Photo documentation may be helpful to document the disease course and response to therapy. In addition, palpation of regional lymph nodes and organs should be performed to rule out lymphadenopathy or organomegaly [50]. A skin biopsy of a representative lesion (in some cases several biopsies are needed) should be performed including immunohistochemistry and TCR gene rearrangement studies. Initial blood work-up should include CBC with differential, liver function tests, LDH, creatinine, electrolytes, and C-reactive protein. Although extremely rare in the pediatric population, but if erythrodermic MF or SS are suspected, blood work-up needs to be extended (TCR gene rearrangement studies and Sézary cell count/flow cytometry) [9, 50]. Radiographic imaging should be performed based on the TNMB stage. For diseases with limited skin involvement (IA, IB) chest x-ray and ultrasonography of the abdomen and regional lymph nodes are usually sufficient [9, 50]. Whole-body imaging is recommended to rule out lymphadenopathy and potential visceral involvement in children staged ≥ IIB. Excisional lymph node biopsy should be performed in those patients with a radiographic node > 1.5 cm [9, 50].

Patients should be staged according to the TNMB staging of MF and SS (Tables 2, 3) [25].

Therapy and prognosis

The treatment modality depends on the disease stage. Table 1 summarizes 17 studies with a total of 366 childhood MF cases, encountered in the English literature (single case reports or studies reporting less than 5 cases where not included). The majority of juvenile MF patients (95 %) had early-stage disease and were therefore treated with skin directed therapies. The most used treatment modality included narrowband-UVB (NB-UVB) alone or in combination with topical steroids. PUVA was used as second line treatment in some cases or first line therapy for FMF. Topical or oral retinoids were only used occasionally. Only 5 % of children had advanced stage MF, in these cases multiple agents were used, including topical nitrogen mustard, radiotherapy and stem cell transplantation. Novel systemic treatment modalities including the antibody-drug conjugate, brentuximab vedotin and the anti-chemokine receptor 4 monoclonal antibody, mogamulizumab have recently been approved for the treatment of advanced staged MF [51, 52]. Efficacy data of brentuximab vedotin in the pediatric population exist for the treatment of relapsed or refractory Hodgkin’s lymphoma or systemic anaplastic large-cell lymphoma but are still scarce for pediatric MF [53].

Most children with early-stage disease responded well to phototherapy, but relapses were not uncommon.
co-workers published their long-term follow-up data of 28 children receiving phototherapy and found that patients receiving PUVA had fewer relapses compared to those who received NB-UVB [19]. Long term follow-up of pediatric MF patients is recommended to allow early detection of relapses and timely reintroduction of therapy.

Prognosis of childhood MF is generally excellent, since most juvenile MF patients have early-stage disease. It is however noteworthy that advanced MF cases with disease progression leading to death have been reported in children as well (1% of cases included in summary Table 1). For most cases published in the literature follow-up is limited, hampering our ability to predict the intermediate and long-term prognosis. Considering the longer life expectancy of juvenile patients, rigorous long-term follow-up exams – ideally at dedicated centers – are recommended to allow for early detection of disease progression.

One example is a 14-years old patient with granulomatous MF that we have published in 2016, who has initially responded well to phototherapy at six-month follow-up but unfortunately showed disease progression one year after our report was published [54, 55].

**Lymphomatoid Papulosis**

**Epidemiology and clinical presentation**

Lymphomatoid papulosis (LyP) is a chronic disorder that is characterized by a waxing and waning disease course, i.e. it is typically self-regressing [56, 57]. LyP is considered a rare disease and children and adolescents account for only 4–10% of LyP cases [56, 58]. On the other hand, LyP represents the second most common form of CTCL in children [5]. We previously published a systematic review on LyP in children and adolescents aged 0–18 years where 251 patients were identified from the literature including seven own cases [59]. The mean age at diagnosis was 9.3 years (although the reported age at onset of symptoms was on average approximately one year earlier) and the youngest patient was only 11 months old. Comparable to the adult form, LyP is slightly more prevalent in boys than girls 1:1.4 [59].

The lesions can be found on any part of the body and are typically erythematous papules or nodules and only rarely pustules, plaques, papulovesicles or tumors (Figure 2) [59]. The diagnosis of LyP is often delayed and differential diagnoses include scabies, arthropod bites, pityriasis lichenoides, and hydroa vacciniforme [59]. Whether LyP should be considered a benign or malignant disease still remains subject of debate: While the long-term prognosis of LyP remains excellent with a 5-year overall survival close to 100%, between 10–30% of patients will develop a secondary non-Hodgkin lymphoma over the course of their disease [56–58, 60, 61]. In our systematic review, associated lymphomas were reported in 5.6% of the children and adolescents [59].

**Histopathology**

Lymphomatoid papulosis is categorized as a CD30+ LPD [56]. CD30 is a cell surface marker that can be found on T and B lymphocytes but was first identified on Reed-Sternberg cells in Hodgkin lymphoma by Stein and coworkers [62]. CD30 can also be expressed in certain viral infections, germ-cell tumors, and arthropod bites [63]. In our systematic review, 96.3% of the reported biopsies in children showed CD30 expression [59]. Since the initial description of LyP, five major histopathological subtypes (types A to E) have been described [57, 64–66]. Recently,
additional subtypes have been identified and reported: “type F” representing follicular LyP, LyP with a γ/δ phenotype, and 6p25.3 rearrangement [57, 67–69]. The majority of pediatric cases are classified as subtype A (79.1 %) or C (11.9 %) [59]. The high percentage of subtype A may be an overestimation, taking into consideration that over the years the histopathologic classification of LyP has been refined [59]. It is important to note, that the more recently published and rarer subtypes have also been reported in children [59, 65, 70].

**Diagnostic work-up**

Given the clinical and histopathological heterogeneity and overlap with other lesions/diseases, the diagnosis of LyP is always a correlation of the clinical appearance, clinical course and histologic, immunophenotypic, and cytogenetic features [71]. Particularly in cases where the diagnosis is equivocal, it is recommended to refer the patient to a dedicated center with expertise for the diagnostic work-up to permit a short line of communication between clinician and histopathologist as one may not be able to establish the diagnosis without the other.

**Therapy and prognosis**

In view of the self-limiting disease course and the excellent overall prognosis, risks and benefits of therapeutic interventions should be carefully weighted in children. While the majority of children are given one medication (most often topical corticosteroids), our systematic review has identified cases with up to five different modalities including chemotherapy, bexarotene, methotrexate and radiation [59]. An early referral and timely diagnostic confirmation of LyP likely prevents unnecessary treatment regimens. Ideally, LyP is managed by a dedicated CTCL expert as overtreatment should be avoided due to the self-regressing nature of the disease. In many instances topical corticosteroids are sufficient for a symptomatic disease.

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The majority of pediatric cases are classified as subtype A.

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**Figure 2** Distribution and morphology of LyP lesions in children and adolescents. The figure illustrates the distribution (blue/left) and the morphology of LyP lesions (red/right) in children and adolescents according to the numbers reported in our systematic review (Wieser et al. [59]; based on a figure template provided by Smart Servier Medical Art under the CC license).
control as treatment does not appear to have an effect on the overall disease course [58, 59]. Other treatment modalities should be reserved for those patients with a high symptom burden and frequent relapses. Due to the association with lymphomas long-term follow up by a dermatologist experienced in CTCL is warranted as pediatric cases have been reported, where associated lymphomas developed up to 17 years after the initial diagnosis of LyP [59].

Primary cutaneous anaplastic large cell lymphoma

Epidemiology and clinical presentation

Primary cutaneous anaplastic large cell lymphomas (cALCL) are defined as anaplastic large cell lymphomas (ALCL) in the absence of systemic disease as confirmed by the initial staging workup [72]. In children primary cALCL account for 11 % of all cutaneous LPDs [5]. Patients typically present with a large solitary red to brown cutaneous nodule or tumor that may ulcerate with time [57]. Multifocal disease with lesions involving more than one body region or by a lesional area larger than 15x15 cm is present in up to 20 % [1, 57, 73]. The nodules or tumors regress in up to 50 %, but typically do not resolve completely [74]. Fink-Puches and colleagues published 13 cases of children and adolescents with cALCL diagnosed at a median age of 14 (range, 3–19) years with equal distribution between boys and girls [4]. Cases have been reported even in the neonatal period [75]. The clinicopathological features in children appear to be similar to those in adults [4, 5].

Histopathology

Besides LyP, cALCL represents another CD30+ LPD. By definition CD30 is expressed by at least 75 % of the large aberrant lymphocytes in cALCL and the most common phenotypes are CD4+/CD8– and CD4–/CD8+ [5, 57]. As opposed to systemic ALCL, cALCLs usually lack ALK-1 expression. ALK-1 expression indicates rearrangement in the anaplastic lymphoma kinase (ALK) gene, of which t(2;5) and t(1;2) are the most common variants [76]. Generally, secondary cutaneous involvement of systemic ALCL should be considered if a biopsy suggests ALK+ ALCL [5]. Interestingly, however, a case series of six children and several case reports with ALK+ ALCL limited to the skin that completely regressed, have been published [5, 77–79]. Histologically cALCL can have overlapping features with LyP – especially subtypes C and D [5, 57, 64, 80]. McQuitty and coworkers studied the differentiation of CD8+ cALCL from LyP type D in 27 patients. The authors found that the presence of ulceration, epidermotropism with small lymphocytes and marked density of CD30+ large atypical cells extending to the subcutaneous tissue may be indicators that favor a diagnosis of cALCL [80].

Diagnostic work-up

Following the clinical examination and confirmatory biopsy, systemic ALCL should be excluded. The German guidelines for CTCLs recommend full-body imaging and lymph node sonography and state that a PET-CT may be considered [50]. Given the rarity of cALCL, no specific recommendations are available for children.
In the general population, the treatment of choice for solitary primary cALCL lesions is typically surgical excision. When multiple lesions are present, low-dose electron beam radiation can be considered. In some patients adjuvant radiation might be recommended, especially when the surgical margins are not clear [57, 73, 81]. Specific treatment recommendations for children are scarce. Surgical excision has been reported with good response rates [75]. In the series of Fink-Puches and colleagues the overall prognosis in children was good. At a median follow-up of 9.5 months (range, 4–84 months), 50% were disease free and no disease-related deaths were observed [4].

Epstein-Barr virus-positive lymphoproliferative disorders in childhood

Epstein-Barr virus (EBV)-positive LPD in childhood comprise hydroa vacciniforme-like LPD (HV-like LPD) and hypersensitivity reactions to mosquito bites, which are now included in the 2018 update of the WHO-EORTC classification for PCL [2].

Hydroa vacciniforme-like LPD and hypersensitivity reactions to mosquito bites are skin manifestations of chronic EBV infections, predominantly affecting children and adolescents in Central American, South American and certain Asian regions [2, 82–84]. Children affected by these primary cutaneous LPD may progress to systemic EBV-positive T- or natural killer-cell lymphoma [2].

Clinically, HV-like LPD are characterized by blisters, ulcers, crusts and sometimes disfiguring scar formation, along with edema affecting sun-exposed body parts, such as the face and the extremities [82, 83]. Histologically, atypical small-to medium-sized T-lymphocytes infiltrating the epidermis, dermis and subcutis, sometimes showing an angiotropic pattern, are seen on skin biopsies. In addition to the skin manifestation, systemic symptoms including fatigue, fever, lymphadenopathy and hepatosplenomegaly may be seen [82, 85]. Skin lesions may follow a waxing and waning course [84]. Prognosis of reported cases with available long-term follow-up data was dismal, with many children not responding to chemotherapy or radiotherapy and dying of sepsis or liver failure in the course of their disease [82, 84]. Differential diagnoses include other CTCL, especially cutaneous nasal natural killer (NK)/T-cell lymphoma, MF and subcutaneous panniculitis-like T-cell lymphoma [82].

Children with hypersensitivity reactions to mosquito bites present with ulcerative and necrotic lesions at the site of the mosquito bite and may have the same systemic symptoms as patients with HV-like LPD [2].

Funding
Iris Wohlmuth-Wieser received a grant from the Austrian Science Fund (FWF), project number J-4382.

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CME Questions/Lernerfolgskontrolle

1. Which of the following represents the most common primary cutaneous lymphoma found in children and adolescents?
   a) Mycosis fungoides
   b) Lymphomatoid papulosis
   c) Primary cutaneous anaplastic large cell lymphoma
   d) Granulomatous slack skin
   e) Pagetoid reticulosis

d) Biopsies from hypopigmented MF lesions show epidermotropism of small-to-medium-sized lymphocytes and the atypical lymphocytes are predominantly CD8+.
e) Histologically large multinucleated giant cells (immunophenotypically expressing CD68) emperipolesis and loss of elastic tissue are evident.

2. Which of the following is true with regards to the stage at diagnosis in mycosis fungoides (MF) in children and adolescents?
   a) Due to its rarity, MF is often overlooked and the few children that are diagnosed already have visceral organ involvement (M1).
   b) Children diagnosed with MF often have high blood tumor burden with ≥ 1,000/μL Sézary cells with positive clones.
   c) More than 95 % of children are diagnosed at early disease stages with either limited patches or plaques involving < 10 % BSA (IA) or generalized patches/plaques > 10 % BSA (IB).
   d) Disease progression and fatal outcomes have not been observed in children and adolescents.
   e) Children with MF should not be staged according to the ISCL/EORTC staging of MF and Sézary syndrome.

3. Which of the following is true for hypopigmented mycosis fungoides (MF)?
   a) Hypopigmented MF is an uncommon form of MF in children.
   b) Hypopigmented MF in children is characterized by a poor prognosis.
   c) Hypopigmented MF typically presents with indurated patches and plaques often on hair bearing body parts including the face, eyebrows and scalp, along with acniform lesions and alopecia.

4. Which of the following is true with regards to folliculotropic mycosis fungoides (FMF)?
   a) FMF is characterized by the presence of hypopigmented patches or plaques.
   b) FMF is the most common variant of MF observed in children and adolescents.
   c) The features of FMF are typically more pronounced in children and adolescents as compared to adults.
   d) FMF is characterized by neoplastic lymphocytes infiltrating the hair follicles.
   e) The majority of children with FMF are diagnosed in advanced stages of the disease.

5. Which of the following is a typical differential diagnosis of classic mycosis fungoides (MF)?
   a) Vitiligo
   b) Alopecia mucinosa
   c) Pityriasis alba
   d) Postinflammatory hypopigmentation
   e) Atopic dermatitis

6. Which of the following is true with regards to treatment and prognosis of mycosis fungoides (MF)?
   a) The treatment modality typically depends on the disease stage.
   b) In the literature review, the most common treatment for MF was systemic chemotherapy.
   c) The majority of children did not respond to phototherapy.
   d) For the majority of pediatric cases published in the literature long-term data are available.
   e) Advanced stages and fatal outcomes have not been reported in children and adolescents.

7. Which of the following statements is correct with regards to lymphomatoid papulosis (LyP) in children and adolescents?
   a) By definition LyP is a CD4+ lymphoproliferative disorder.
   b) LyP is typically observed in children and adolescents (0–18 years) and only rarely affects people older than 18 years.
   c) The diagnosis of LyP is often delayed and common misdiagnoses include scabies, arthropod bites, pityriasis lichenoides, and hydroa vacciniforme.
   d) The clinical examination is unreliable, and the diagnosis is exclusively established by histopathologic work-up.
   e) Due to the disease course, the initial treatment modality should be systemic in children and adolescents.

8. Which of the following statements is true with regards to disease course, prognosis and follow-up of lymphomatoid papulosis in children and adolescents?
   a) LyP is a chronic disorder that is characterized by a waxing and waning disease course.
   b) LyP typically presents as a large solitary nodule or tumor that typically ulcerates over time.
   c) LyP has a poor overall prognosis with a dismal 5-year overall survival rate.
   d) LyP in adults is associated with other lymphomas, but this does not apply to pediatric patients with LyP.
   e) LyP should be treated by a Dermatologist experienced in CTCL,
but once the lesions disappear the patient can be discharged and does not need follow-up.

9. Which of the following statements is true with regards to anaplastic large cell lymphomas (ALCL)?
   a) Primary cutaneous ALCL can be differentiated from LyP by CD30 expression.
   b) Primary cutaneous ALCLs must be differentiated from systemic ALCLs.
   c) Primary cutaneous ALCL typically presents as a multifocal disease with lesions involving more than one body region.
   d) The lesions in primary cutaneous ALCL are typically small papules or pustules.
   e) Due to the nature of the disease no further work-up (i.e. no imaging studies) should be performed.

10. Which of the following statements is true with regards to the treatment of primary cutaneous anaplastic large cell lymphomas?
   a) The treatment of choice for solitary lesions is typically topical corticosteroids.
   b) The treatment of choice for solitary lesions typically consists of a combination of systemic antibiotics and corticosteroids.
   c) The treatment of choice for solitary lesions is typically systemic chemotherapy.
   d) The treatment of choice for solitary lesions is typically surgical excision.
   e) Radiation should be avoided due to the high dose that is required causing significant systemic side effects.