Leukaemia cutis as a specific skin involvement in chronic myelomonocytic leukaemia and review of the literature

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Abstract: The skin involvement of myeloid leukaemia is conventionally divided into specific malignant lesions and non-specific benign lesions, and these categories are also applicable in chronic myelomonocytic leukaemia (CMML). According to the 2016 World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues, CMML is defined as a myeloid neoplasm with characteristics of myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs). As a specific cutaneous sign of extramedullary infiltration, leukaemia cutis (LC) is a rare occurrence in patients with CMML, and only approximately 89 cases have been reported in the literature thus far. The clinical features of LC are varied, and LC in CMML exhibits heterogeneous histopathologic features, with manifestations as cutaneous nodules or papules that are composed of blast cells showing either granulocytic or monocytic differentiation. Skin biopsy and further immunohistochemical examination are essential at the time of diagnosis to evaluate pathological type and determine the clinical course. Generally, once diagnosed as LC in CMML, this unusual skin lesion might be an indicator of transformation to acute myeloid leukaemia (AML) and is associated with a poor prognosis. The main treatment is allogeneic stem cell transplantation (ASCT). Therefore, early diagnosis and accurate identification have important therapeutic and prognostic significance in CMML patients with skin infiltration.

Keywords: Chronic myelomonocytic leukaemia (CMML); skin involvement; leukaemia cutis (LC); prognosis; extramedullary infiltration

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Introduction

CMML often presents with sustained (>3 months) peripheral blood (PB) monocytosis [≥1×10⁹/L; monocytes ≥10% of the white blood cell (WBC) count] along with dysplastic features in the bone marrow (BM) and has an inherent risk for transformation to acute myeloid leukaemia (AML). CMML is now subdivided into three types (CMML-0, 1, 2) depending on the number of blasts and promonocytes found in the PB or BM. Since CMML is a subtype of MDS or MPN, it is divided into myelodysplastic CMML (MD-CMML, WBC <13×10⁹/L) and proliferative CMML (MP-CMML, WBC ≥13×10⁹/L) based on the WBC count, according to the French-American-British (FAB) recommendations (1). The skin involvement of CMML can be both specific, such as neoplastic infiltration (leukaemia cutis, LC), and non-specific (e.g., opportunistic infections, neutrophilic and granulomatous dermatoses, and
LC is defined as a specific cutaneous involvement of myeloid or lymphoid tumour cells, resulting in clinically identifiable cutaneous lesions, which mostly occur in patients with AML and rarely in those with chronic myeloproliferative diseases (3), especially CMML. The occurrence of skin lesions may be the result of various features of CMML and heralds its progression to acute leukaemia. In this article, we review the literature and discuss the incidence, clinical characteristics, diagnosis, pathological features, treatment and prognostic value of LC in CMML. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-19-2882).

**Data source**

We searched the key subject terms “chronic myelomonocytic leukaemia”, “skin involvement”, and “leukaemia cutis” in the PubMed database from 1983 to September 2019. Most of the articles were case reports, from which we collected data for further discussion, and all cases were diagnosed as CMML with LC (Table 1).

**Epidemiology and pathogenesis**

LC is a rare specific skin involvement of leukaemia occurring in 10% to 15% of patients with AML; most cases occur in patients with AML, especially acute monocytic leukaemia, and approximately 1% of patients with chronic lymphocytic leukaemia (3). Moreover, the incidence of LC seems to be higher among children than adults, particularly in infants with myeloid leukaemia (3,28,29). In contrast, CMML mostly occurs in the elderly population, with an incidence of approximately 4 cases per 100,000 persons per year. The median age ranges from 71 to 74 years, with a predominance in males, and the male-to-female ratio is approximately 1.5–3:1 (1). Due to the low incidence of CMML, skin involvement in CMML is relatively rare, especially LC. Bénet et al. reported 173 patients with myeloid leukaemia with LC from their database of 9 centres in France between 1992 and 2008; only 19 (11%) patients had CMML (30). In Mathew’s study, 11 of 108 patients (10%) with CMML were diagnosed with LC at the Moffitt Cancer Center [2003–2010] (17). The epidemiology of LC in CMML is not well known at present; only 24 publications about LC occurring in CMML were identified when we searched the English literature between 1983 and 2019 (7-30). The available data from these 89 previous cases of CMML with LC are summarized in Table 2. The actual incidence might be slightly higher than the number of cases collected in this study because the failure to perform skin biopsy may lead to the misdiagnosis of LC as other types of lesions. There were 67 males and 22 females, with a mean age of 70 years (range, 5 to 95 years). Overall, LC can precede, follow or occur concomitantly with systemic leukaemia, as well as CMML, and all three have been described in isolated or multiple case studies. In general, 62.9% (56/89) of the cases occur after a diagnosis of CMML has been established, whereas nearly one-third of the skin lesions occur simultaneously at diagnosis. Rarely (5.7% of cases), skin involvement occurs several months or years before PB or BM abnormalities are detected and before the onset of systemic symptoms; this is so-called “aleukaemic leukaemia cutis”, which eventually develops into AML and has a relatively worse prognosis (31,32).

The molecular pathological mechanism underlying the invasion of leukaemic cells into the skin is not very clear so far. The expression of T-cell antigens and CD56 on blast cells may be associated with cutaneous involvement (33,34). In a study in 2008, Cho-Vega and colleagues proposed the hypothesis that memory T-cells, different chemokine receptors and specific adhesion molecule receptors might play an intermediate role in causing leukaemic cells to migrate into the dermis; this hypothesis still needs clarification through further research (3).

**Clinical characteristics**

Patients with CMML may present with a variety of cutaneous manifestations at any stage of the disease. The skin lesions are generally divided into specific and non-specific lesions: the former is the result of the direct invasion of neoplastic leukocytes (leukaemia cells) into the epidermis, dermis, or subcutaneous tissues, and includes LC and its subcategory leukaemic vasculitis, which involves leukaemic cells infiltrating and destroying blood vessels within the dermis (2). Since LC occurs in different types of leukaemia, it can have various clinical appearances (18,20,26). We found that the majority of these 89 CMML cases in the literature presented as violaceous or red-brown nodules, papules, plaques of varying sizes, and maculo-papular rash, while the number of cases with painful or pruritic rash, pustules and ulcers were fewer. Furthermore, the skin lesions were localized or disseminated and could be located in any site of the body, mostly involving the trunk and lower extremities, followed by the face, arms, scalp...
Table 1 Clinical manifestations and outcomes of CMML patients with leukemia cutis reported in the literature (n=89, 1983–2019)

| No. of cases | Sex/age (year) | Presentation of skin lesions/location | Cytogenetics | Organomegaly | Treatment | Response of skin lesions to treatment | Progression(1) | Outcomes | References |
|--------------|----------------|---------------------------------------|--------------|--------------|-----------|--------------------------------------|----------------|----------|------------|
| 4            | M:2, F:2; mean age: 68 | Papules [3]; purpura [1]; chest [1]; * [3] | Normal       | Hepatomegaly [2]; splenomegaly [2] | Steroids, polychemotherapy | Resistant | Yes [1]; * [3] | Dead (4) |
| 1            | F/44            | Erythematous papules/leg *              | *            | *            | RT; hydroxyurea | Resistant | Yes (chloroma) | Dead (5) |
| 1            | M/74            | Nodules/widespread *                   | *            | Lymphadenopathy | Polychemotherapy | Yes (AMML) | Dead (6) |
| 4            | M:1, F:3; mean age: 81 | Papules [1]; nodules [1]; pruritic rash [2]; extremities, trunk [3]; widespread [1] | *            | *            | Cytarabine, razoxane etoposide; RT | Resistant [1]; PR [2]; CR [1] | * | Dead [3]; alive [1] |
| 1            | M/68            | Nodules/face, chest back *              | *            | Splenomegaly | Cyclophosphamide, vincristine hydroxyurea (3 mon) | Relapse | Yes (AMML) | Dead (8) |
| 1            | M/69            | Pruritic nodules/chest, back, scalp *  | No           | Minocycline, Ara-C | PR | Yes | Dead (9) |
| 4            | M:3, F:1; mean age: 55 | *                                      | Normal [3]; abnormal [1] | *            | Polychemotherapy | * | * | Dead (10) |
| 1            | M/57            | Erythematous papules/trunk, extremities | *            | Lymphadenopathy | Mitoxantrone, Ara-C, intrathecal methotrexate | * | No | Dead (11) |
| 1            | M/56            | Purple plaques/forehead, widespread *  | *            | Parotid gland swelling | Daunorubicin, Ara-C, etoposide; RT | Relapse, resistant | Yes (AML-M4) | Dead (12) |
| 1            | M/59            | Pruritic nodules/back, chest, face, scalp | *            | No            | Polychemotherapy; RT | Relapse | * | * | (13) |
| 1            | M/65            | Erythematous nodules/chest, abdomen Normal | Testicular swelling | Etoposide; RT | Relapse (4 mon) and resistant | Yes (AML) | Dead (14) |
| 1            | F/95            | Red nodules/trunk, legs Trisomy 8 *    | *            | Hydroxycarbamide; palliative care | Resist | * | (15) |
| 1            | M/64            | Erythematous papules, nodules/face, perioral area | *            | *            | Hydroxyurea | * | Yes (AML) | Dead (16) |
| 11           | M:9, F:2; mean age: 63 | Erythematous rash, plaques, pigmented nodules/location(*) | Normal [4]; Abnormal [2]; Lymphadenopathy [1]; CNS involvement [1], * [7] | Splenomegaly [2]; Lymphadenopathy [10]; stem cell transplant [1] | Polychemotherapy | * | Yes [4]; No [6]; * | Dead [7]; alive [3]; * | (17) |
Table 1 (continued)

| No. of cases | Sex/age (year) | Presentation of skin lesions/location | Cytogenetics | Organomegaly | Treatment | Response of skin lesions to treatment | Progression | Outcomes | References |
|--------------|----------------|---------------------------------------|--------------|--------------|-----------|---------------------------------------|-------------|----------|------------|
| 42           | M:35, F:7/; Mean age:71 | Papules, nodules, plaques, eruption [33]; ulcers [3]; others [6]; * [1] | Normal [1]; * Abnormal [7]; * [24] | | Polychemotherapy [25]; radiotherapy [2]; local steroid [3]; none [4]; * [8] | Resistant [8]; PR [13]; CR [11]; * [10] | Yes [6]; no [20]; * [16] | Dead [19]; alive [22]; * [1] |
| 4            | M:3; F:1; /mean age: 77 | Papules, nodules [3]; pustule [1]/trunk, limbs [1], face [1], back [1], widespread [1] | * | * | Chemotherapy [2], observation [2]; RT | * | Yes [1] (AMoL); no [3] | Dead (19) |
| 1            | M/75              | Scarred plaques/feet, arms, legs, umbilicus | * | * | | PR | * | Alive (20) |
| 1            | M/61              | Pruritic rash/trunk, limbs, face | Abnormal | Hepatomegaly; splenomegaly | Polychemotherapy | CR | Yes (AML) | Dead (21) |
| 2            | M/70              | Popular rash/hand, forearms, trunk, thighs | Normal | * | | * | * | Yes [1] (AML); * [1] | Dead [1]; alive [1] |
| 1            | M/67              | Erythematous papules/scalp, neck, groin | Normal | Hepatomegaly; splenomegaly | Clofarabine | Resistant | Yes | Dead (23) |
| 1            | M/81              | Erythematous nodules/widespread | * | Hepatomegaly; splenomegaly | 5-azacytidine, palliative care | Resistant | Yes (AML) | * | (24) |
| 1            | M/68              | Multiple papules/trunk, extremities | * | * | | * | * | Dead (25) |
| 1            | F/75              | Erythematous, ulcerated lesions/finger, feet, nose | * | No | Steroid | PR | * | * | (26) |
| 2            | F/60              | Red nodules; rash/chest, back, right limbs | Normal | No | Decitabine, chemotherapy; Decitabine | Resistant | Yes [2] (AMoL) | Dead (27) |

*, not clearly described in the literature. M, male; F, female; Age, mean age; BM, bone marrow; PB, peripheral blood; ①, transformation to acute myelogenous leukaemia (AML), acute myelomonocytic leukaemia (AMML), acute monocytic leukaemia (AMoL) or disease progression; CNS, central nervous system; Ara-C, cytosine arabinoside; PR, partial response; CR, complete response;
Table 2 Summary of the main clinical data of 89 cases in the literature

| Main clinical data                                      | All patients, n (%) |
|---------------------------------------------------------|---------------------|
| Total of the number of cases                            | 89                  |
| Median age(years)                                       | 70                  |
| Sex                                                     |                     |
| Male                                                    | 67 (75.3)           |
| Female                                                  | 22 (24.7)           |
| Common findings of presentation                         |                     |
| Papules, nodules, or plaque                             | 76 (85.4)           |
| Ulcer                                                   | 4 (4.5)             |
| Pustule                                                  | 1 (1.1)             |
| Others (such as unique subcutaneous swelling)           | 6 (6.7)             |
| Data not available                                      | 2 (2.2)             |
| Common findings of location                             |                     |
| Extremities, trunk, chest or widespread                 | 72 (80.9)           |
| Other locations (face, nose, scalp, neck, feet, finger) | 10 (11.2)           |
| Data not available                                      | 7 (7.9)             |
| Chronology of skin lesions                              |                     |
| Before diagnosis of CMML                                | 5 (5.7)             |
| Concomitant with diagnosis of CMML                      | 26 (29.2)           |
| After diagnosis of CMML                                 | 56 (62.9)           |
| Data not available                                      | 2 (2.2)             |

Table 2 (continued)

| Main clinical data                                      | All patients, n (%) |
|---------------------------------------------------------|---------------------|
| Extramedullary (EM) manifestations                      |                     |
| Hepatosplenomegaly or lymphadenopathy                   | 64 (71.9)           |
| Central nervous system involvement                     | 1 (1.1)             |
| Testicular swelling                                     | 1 (1.1)             |
| Parotid gland swelling                                  | 1 (1.1)             |
| None                                                    | 5 (5.6)             |
| Data not available                                      | 17 (19.1)           |
| Duration from skin lesion to disease progression or death(months) |         |
| ≤5                                                     | 30 (33.7)           |
| 6-10                                                   | 6 (6.7)             |
| 10-20                                                  | 28 (31.5)           |
| 23                                                     | 16 (18.0)           |
| Data not available                                      | 9 (10.1)            |
| Treatment                                               |                     |
| Chemotherapy ± radiotherapy or local steroid            | 72 (80.9)           |
| Stem cell transplant                                    | 1 (1.1)             |
| None or palliative care                                 | 6 (6.7)             |
| Data not available                                      | 10 (11.2)           |

CMML, chronic myelomonocytic leukaemia.

and neck (Table 2). Non-specific skin lesions occur in up to 40% of patients with leukaemia (3), covering a variety of complex manifestations that are mostly attributable to a number of nonmalignant causes: infectious aetiologies, such as chronic fungal infections (thrush), bacterial infections (Staphylococcus aureus) (35) and viral infections (herpes simplex); connective tissue disorders, such as systemic lupus erythematous, sarcoidosis, and neutrophilic dermatoses [Sweet syndrome (36) and pyoderma gangrenosum (37,38)]; and drug eruptions, resulting in unidentifiable cutaneous lesions that make it difficult to clinically distinguish LC from other skin lesions. Of course, a similar distribution of skin lesions should also be considered, which may the result of neoplastic factors, such as the metastasis of visceral malignancies, lymphoma, Kaposi sarcoma, basal cell carcinoma and squamous cell carcinoma (39). Skin biopsy and further immunohistochemical examinations are the main differential diagnosis tools at present (3,39,40). In addition, we found that most patients with LC generally also have other types of extramedullary symptoms, which may be associated with a worse prognosis and shorter survival (41). The most common locations include the liver, spleen and lymph nodes, whereas the involvement of the central nervous system and other sites are rare (Table 2).

Diagnosis

The diagnosis of LC is mainly based on the clinical characteristics and histopathologic features of the skin lesions, including the cytologic features, and the immunophenotype of the infiltrative tumour cells is the
most important, as it can further distinguish CMML from other subtypes of leukaemia. In addition, medical history, PB findings, immunohistochemistry, flow cytometry, fluorescence in situ hybridization, and molecular analysis of BM biopsy are also helpful in confirming the diagnosis (25,40). However, in the absence of a clinical history of leukaemia, which we called aleukaemic LC, conventional diagnostic tools for haematologic malignancies have little value, and morphologic and immunohistochemical analysis of the skin lesions are critical for the diagnosis (42). Therefore, we always make every effort to obtain a tissue diagnosis unless there is a contraindication in the clinical course. The diagnostic process is shown in the Figure 1.

**Histopathologic features**

As a direct invasion of malignant myeloid blasts into the skin, LC in CMML exhibits heterogeneous histopathologic features, with manifestations as cutaneous nodules or papules that are composed of blast cells showing either granulocytic or monocytic differentiation (42). In the largest retrospective analysis study to date, Vitte et al. divided 42 skin biopsy specimens of CMML patients with LC into four distinctive groups according to the morphological immunophenotypic characteristics of the infiltrating tumour cells: (I) myelomonocytic cell tumours (MMCTs, 43% of CMML patients) consisting of myeloid blasts that were positive for CD68 and/or myeloperoxidase (MPO) but negative for dendritic cell markers; (II) mature plasmacytoid dendritic cell (PDC) proliferations (MPDCPs, 38% of CMML patients) consisting of mature PDCs positive for CD123, TCL1, and CD303; (III) blastic PDC neoplasms (BPDCNs, 10% of CMML patients) mainly composed of monomorphous medium-sized blast cells that were positive for CD4, CD56, CD123 and TCL-1; and (IV) blastic indeterminate dendritic cell tumours (BIDCTs, 10% of CMML patients) consisting of large blast cells that were positive for CD1a, CD4, CD13, CD33, CD56 and S100 protein but were negative for langerin, CD123 and TCL-1. The authors emphasized that PDCs could be a precursor of indeterminate dendritic cells (IDCs) and that IDCs could be a precursor of Langerhans cells, suggesting that the dendritic cell lineage plays an important role in the spectrum of lesions (18). PDCs, also called “plasmacytoid T-cells” or “plasmacytoid monocytes”, were discovered very early in CMML (43,44) and are derived from the differentiation of myelomonocytic cells (45). Magro et al. described the clinical and pathological features of 11 patients with cutaneous myeloid dendritic cell dyscrasia,

Figure 1 Flow chart with a brief description of the diagnostic process for CMML patients with skin involvement. *, 2016 WHO recommended diagnostic criteria for CMML. IHC, immunohistochemistry; FCM, flow cytometry; FISH, fluorescence in situ hybridization; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukaemia.
two of whom had CMML (22). Since then, cases of similar pathological types of CMML patients with skin involvement have been reported sporadically in the literature (26). There have also been solitary reports of skin infiltration of “tumour-forming PDCs” and “indeterminate cells” expanding the spectrum of skin lesions in CMML with LC (21,23), which remain to be fully elucidated in terms of the pathological features and mechanism in future research. Interestingly, the immunophenotype of the skin lesions may be discordant with the immunohistochemical profile in the BM (24,42).

**Prognosis**

CMML is a clonal myeloid neoplasm with features of MDS and MPNs and has an inherent risk for transformation to AML. The extramedullary involvement of AML is most notably present as myeloid sarcoma (also termed granulocytic sarcoma, chloroma, or myeloblastoma), central nervous system leukaemia and LC (46). LC, as one of the main forms of extramedullary myeloid neoplasm, rarely occurs in CMML compared to in AML. Thus far, a variety of chromosomal abnormalities have been reported in patients with AML with extramedullary involvement (41), and although AML with t(8;21) has been classified into a favourable-risk group, it still has a higher incidence of extramedullary involvement and has a worse prognosis compared to other AML subtypes (47). In CMML, numerous prognostic models have been used to predict survival, such as the MD Anderson prognostic scoring system (MDAPS), CMML-specific prognostic scoring system (CPSS), Mayo Prognostic Model (MPM), Groupe Francais des Myelodysplasies (GFM), and Mayo Molecular Model (MMM) (48). Among these, the CPSS categorizes patients into three groups: high risk (trisomy 8, chromosome 7 abnormalities, or complex karyotype), intermediate risk (all chromosomal abnormalities, except for those in the high- and low-risk categories), and low risk (normal karyotype or –Y), with 5-year overall survival (OS) rates of 4%, 26%, and 35%, respectively (1). However, it is not clear whether cytogenetic abnormalities or gene mutations are related to the prognosis of CMML with LC, and related reports are very rare (Table 3). In Mathew’s study with 108 CMML patients, the overall median survival of 11 patients with LC was much shorter (28.2 months) than that of the remaining 97 patients who never developed LC (44 months); the study concluded that the specific skin lesions could be a predictor of disease progression or potential transformation to AML and were associated with a worse prognosis (17). Furthermore, a more contemporary study of 42 CMML patients with LC found that the BIDCT subtype had a worse prognosis compared to the other three groups (18). From the above study and previous solitary case reports, we found that approximately 50% (6/12) of patients with chromosomal abnormalities experienced conversion to AML (Table 3). Data on gene mutations in CMML with skin infiltration are even rarer in the literature. Skin pathology showed IDC tumours with KRAS-positive results, as reported by Loghavi et al. (23) Moreover, Federmann et al. reported three CMML patients with granulomatous dermatitis accompanied by SRSF2 mutation, and whether the SRSF2 mutations contributed to the development of granulomatous dermatitis in the patients still needs to be elucidated (49). A 58-year-old CMML patient seen in our department in 2016 presented with LC as an initial manifestation accompanied by TET2 positivity; this patient eventually died due to transformation to AML in just three months (27). The most frequent genetic mutations in CMML include TET2 (~60%), SRSF2 (~50%), and ASXL1 (~40%), with only frameshift and nonsense ASXL1 mutations independently and adversely impacting OS (50), whereas TET2 and SRSF2 mutations are associated with prognosis (48). Moreover, TET2 mutations in the absence of clonal ASXL1 mutations (ASXL1wt/TET2mt) had a favourable impact on OS in a recent study, and the exact mechanism behind this interaction is unclear (51). The probable reason is that TET2 mutations correlate with changes in DNA methylation in CMML, which lead to better responses to hypomethylating agents (52).

In summary, LC has most often been described as a predictor of disease progression and is associated with worse survival outcomes compared to those of patients without LC. Different pathological subtypes of LC have different prognoses. The relationship between cytogenetic or molecular abnormalities and the prognostic value of LC in CMML needs to be fully studied in large-sample clinical trials.

**Treatment**

For LC, as the manifestation of the extramedullary infiltration of leukaemia, the treatment is aimed at eradicating the primary underlying disease because leukaemic cells in the BM will continue to reseed the skin if the BM is not in remission (40). Allogeneic stem cell
transplantation (ASCT) is a unique potentially curative option for CMML regardless of skin involvement. However, due to the rarity of LC in CMML, which predominantly occurs in older patients with comorbidities, ASCT still remains controversial; only a minority of patients are candidates for transplantation, and few patients benefit from it (1). When transplantation is not feasible, the main treatments for MP-CMML are hypomethylating agents (such as azacitidine and decitabine), cytoreductive therapy (hydroxyurea and other cytotoxic drugs), and supportive care, including erythropoiesis-stimulating agents and transfusions; MD-CMML patients are usually managed as are those with MDS (53). When the BM is in remission but LC is persistent, long-term control of skin involvement is critical to effectively prevent blasts reseedig from the BM. Therefore, radiotherapy (RT), such as total skin electron beam (TSEB) therapy for diffuse skin involvement, can be an important part of treatment (54-56). There is no evidence that RT confers any benefit when patients obtain a complete response in the BM and skin after chemotherapy, although local RT for skin lesions is sometimes used for palliative care (56). Moreover, for aleukaemic LC, which predates abnormalities of the PB and BM, some experts recommend that intensive systemic chemotherapy and RT can be used, based on the limited literature (41,57). Given the excessive toxicity, caution should be used to avoid overlapping RT

| Reference        | Age/Sex | Chromosome abnormality                                                                 | Genetic mutations | Progression† | EM                                                                 |
|------------------|---------|---------------------------------------------------------------------------------------|-------------------|--------------|----------------------------------------------------------------------|
| Longacre et al.  | 42/F    | 46.XX,der(3),t(8;16)(p11.2;q33.3)                                                     | *                 | *            | *                                                                  |
| (10)             | 62/M    | 47.XY,+19,iso10                                                                       | *                 | *            |                                                                    |
| Mahmood et al.   | 95/F    | Trisomy 8                                                                             | *                 | *            |                                                                    |
| (15)             |         |                                                                                       |                   |              |                                                                    |
| Mathew et al.    | 71/M    | 45.XY,-7[20]                                                                          | *                 | AML          |                                                                    |
| (17)             | 66/M    | 46.XY,del(11)[13]/47.XY,del(11),+21[8]                                               | *                 | No           |                                                                    |
| 74/M             | 47.XY,+mar[7]/49.XY,+11,+2mar[2]/49.XY[11]                                            | *                 | AML          |                                                                    |
| 69/M             | 46.XY,t(15;17)[20]                                                                    | *                 | CNS          |                                                                    |
| 68/F             | 46.XX,t(1;5)[13]/46.XX[11]                                                           | *                 | AML          |                                                                    |
| Vitte et al.     | 62/M    | 46.XY,del(20)[9]/46.XY[14]                                                           | *                 | No           |                                                                    |
| (18)             | 76/M    | 47.XY,+8[12]/46.XY[13]                                                                | *                 | AML          |                                                                    |
| 5/M              | 46.XY,t(5;13)[q13-q15;q12-q13],add(6)[q13]                                           | *                 | No           |                                                                    |
| 65/M             | 46.XY,del(13)[q14q22][20]                                                            | *                 | No           |                                                                    |
| 60/M             | 46.XY,del(7)[q11.2][13]/47.XY,+21[1]/46.XY[8]                                        | *                 | No           |                                                                    |
| 83/M             | 47.XY,dup[3][q21q21],+8[6]/46.XY[17]                                                | *                 | AML          |                                                                    |
| 59/F             | 47.XX,+8[25]                                                                          | *                 | No           |                                                                    |
| Dargent et al.   | 61/M    | 47.XY,+13[10]/46.XY[10]                                                               | *                 | AML          | Hepatomegaly; splenomegaly                                          |
| (21)             |         |                                                                                       |                   |              |                                                                    |
| Loghavi et al.   | 67/M    | 46.XY[20]                                                                             | KRAS(+)           | Monocytosis   | Hepatomegaly; splenomegaly                                          |
| (23)             |         |                                                                                       |                   |              |                                                                    |

*, not clearly described in the literature. M/F, male or female; 1, transformation to acute myelogenous leukemia (AML) or disease progression; EM, Extramedullary manifestations; CNS, central nervous system; JMML, Juvenile myelomonocytic leukemia; CMML, chronic myelomonocytic leukaemia.
and intensive chemotherapy, especially TSEB (56,58). Recently, in terms of the effectiveness of different doses of RT for the treatment of LC, Elsayad et al. conducted a cohort study and found that patients with AML had a better survival rate than patients with other types of leukaemia (59). Nevertheless, we found that the skin lesions of CMML generally did not respond well to RT in previous case reports, and even if the lesions did initially respond rapidly to RT, the lesions recurred after a short period, especially as the disease progressed. This finding indicates that CMML patients with LC have a predisposition to extramedullary relapses. Although there are many treatments for CMML with LC, the response rates and survival rates following therapy are largely unsatisfactory (17). Therefore, further research into new therapy regimens and subsequent clinical trials are encouraged.

Conclusions

We reviewed the literature on CMML with LC, analysed the clinical and histological characteristics of the disease and underscored the importance of the timely and accurate identification of suspected skin lesions. CMML with LC has a high risk of conversion to AML, and the high mortality rate requires coordination of care by dermatologists, oncologists, and pathologists in the clinical setting. The early diagnosis of LC followed by the prompt initiation of aggressive chemotherapy aimed at eradicating the underlying haematological malignancy may improve the prognosis of leukaemic transformation in CMML. Skin biopsy is mandatory to differentiate between specific (malignant) and non-specific (nonmalignant) lesions. While these currently available treatments can improve patient symptoms, they largely fail to modify the disease evolution and prognosis. Improving the understanding of the molecular pathogenesis of LC in CMML will hopefully lead to the exploration of novel potentially curative therapeutic regimens.

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