Positron emission tomography computed tomography features of monomorphic epitheliotropic intestinal T-cell lymphoma

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ABSTRACT

Objective: To define the positron emission tomography/computed tomography (PET/CT) features of monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), a rare malignancy in European and North American populations and the most common form of primary intestinal T-cell lymphoma in Asian populations.

Methods: 18F-fluorodeoxyglucose (FDG) PET/CT findings of a cohort of MEITL patients were retrospectively analyzed.

Results: Eight men and four women with MEITL investigated by PET/CT at diagnosis and relapse were retrospectively analyzed. On presentation, the primary involved sites were the small bowel (N = 8), large bowel (N = 2), stomach (N = 1) and small and large bowels (N = 1). The uninvolved small bowel did not show increased FDG-avidity to suggest enteropathy. On presentation, lymph nodes and other organs were involved in seven cases (58%). The primary lesions were hypermetabolic except in one case, where the colonic lesion was eumetabolic. At relapse, the stomach and large bowel might be involved even if the primary tumours arose from the small bowel, and multiple extra-intestinal metastases occurred. Interestingly, thoracic structures and the brain were frequently involved (50% and 25% respectively).

Conclusion: These findings showed that in contrast to classical enteropathy-associated T-cell lymphoma, where the small bowel is the exclusive primary site (owing to its origin from coeliac disease) and distant metastases even during relapse are exceptional, MEITL might on presentation and during relapse involve any part of the gut, and metastasize to multiple extra-intestinal sites.

KEYWORDS
Monomorphic epitheliotropic intestinal T cell lymphoma; positron emission tomography computed tomography

Introduction

Primary T-cell lymphoma of the gastrointestinal tract is a very rare and aggressive intestinal tumour of intraepithelial T-lymphocytes, accounting for <1% of all lymphomas [1]. There are two different types, enteropathy-associated T-cell lymphoma (EATL, previously referred to as classical EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL, previously referred to as EATL type II) [2]. EATL evolves from refractory coeliac disease. Therefore, pathological features of enteropathy including villous atrophy and crypt hyperplasia are found in the lymphoma [1]. It constitutes 80% of intestinal T-cell lymphomas in European and North American populations, particularly in patients of North European descent. However, because coeliac disease does not exist in Asian people, EATL is unknown in this population.

Monomorphic epitheliotropic intestinal T-cell lymphoma is the other type of primary intestinal T-cell lymphoma [2]. It accounts for the remaining 20% of cases in European and North American populations, particularly in Hispanic patients [1,2]. It is the exclusive form in Asia [3–6]. Pathologically, lymphoma cells are medium-sized and monomorphic, expressing characteristically CD8, CD56 and MAT kinase [6]. A significant proportion expresses the gamma delta T-cell receptor [3,4]. This lymphoma is not aetiologically or pathologically related to enteropathy [7]. Therefore, in the revised World Health Organization classification of lymphoid malignancies [2], MEITL has been designated as a separate clinicopathologic entity distinct from EATL.

Positron emission tomography/computed tomography (PET/CT) is currently considered the standard imaging modality for the diagnosis, staging and response assessment in Hodgkin lymphoma and other aggressive B-cell lymphomas [8]. However, the role of PET/CT in less common lymphomas, particularly T-cell lymphomas, remains to be defined.

Data of PET/CT in intestinal T-cell lymphomas are very scanty, and the few cases previously reported were all EATL [9–11]. Because MEITL is now a distinct entity, there is a clear need to define its imaging features. In this study, we report the PET/CT findings of a cohort of MEITL patients, so that more can be known for this new and rare disease entity.

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Patients and methods

Patients

Consecutive patients with MEITL (their previous diagnostic label would have been type II EATL) treated between January 2008 and July 2016 were studied. The diagnosis was based on typical histopathological and immunophenotypical features \[1,2\]. Standard clinical and biochemical evaluations for staging and response assessment were undertaken. Treatment protocols evolved over this period and were heterogeneous.

Positron emission tomography/computed tomography protocol and analysis

Details of PET/CT protocol and analysis have been described previously \[12,13\]. Briefly, whole-body \(^{18}\)F-fluorodeoxyglucose (FDG) PET/CT from skull base to the upper third of the thighs was performed with a dedicated combined PET/CT scanner. Activity of FDG was 4.8 MBq kg\(^{-1}\), with an uptake time of 60 min. PET images were analyzed visually and quantitatively. Positive uptake was defined as increased metabolic activity in locations incompatible with normal anatomy or anatomical variant. Responses were assessed according to the 5-point Deauville score (DS). DS of \(\leq 3\) was considered to represent metabolic response. Standardized uptake value (SUV) was measured by normalization to the injected dose and lean body mass. Areas with maximum SUV (SUV\(_{\text{max}}\)) were identified as index lesions. For post-treatment evaluations, change in SUV\(_{\text{max}}\) (\(\Delta\)SUV\(_{\text{max}}\)) was defined as \((\text{SUV}_{\text{max}} \text{ at pre-treatment} - \text{SUV}_{\text{max}} \text{ at post-treatment})/\text{SUV}_{\text{max}} \text{ at pre-treatment}\); regardless of whether the lesion with SUV\(_{\text{max}}\) at post-treatment corresponded to the pre-treatment index lesion.

Results

Patients

Thirteen patients with MEITL were treated. One patient did not have PET/CT scan performed. Twelve patients (8 men, 4 women) at a median age of 56 (39–70) years were analyzed (Table 1). Staging systems developed specifically for gastrointestinal lymphomas classified more patients as having advanced tumour (Lugano, stage II\(_2\)–IV: 50%; Manchester, stage IIb–IV: 58%); which probably better reflected the actual disease extent than the Ann Arbor staging system (stage III–IV: 33%).

| Case | Sex | Age | Presentation | Ann Arbor | Lugano | Manchester | Bone marrow | IPI | PIT |
|------|-----|-----|--------------|-----------|--------|------------|-------------|-----|-----|
| 1    | M   | 44  | Abdominal pain | I         | I      | Ia         | Negative    | 0   | 0   |
| 2    | M   | 50  | Abdominal distension | II       | II\(_E\) | Iib        | Negative    | 1   | 1   |
| 3    | M   | 55  | Ascites, intestinal obstruction | IV       | IV     | IV         | Negative    | 3   | 1   |
| 4    | F   | 57  | Abdominal pain | II       | II\(_E\) | Ic         | Negative    | 2   | 1   |
| 5    | M   | 39  | Diarrhea | IV       | IV     | IV         | Negative    | 3   | 1   |
| 6    | F   | 61  | Abdominal pain, diarrhoea | I       | I      | Iib        | Negative    | 2   | 2   |
| 7    | F   | 51  | Intestinal perforation | III      | IV     | III        | Negative    | 2   | 1   |
| 8    | F   | 70  | Abdominal pain | I       | II\(_E\) | Iib        | Negative    | 2   | 2   |
| 9    | M   | 51  | Diarrhoea, weight loss | II       | II\(_{a}\) | Iia        | Negative    | 0   | 0   |
| 10   | M   | 65  | Gastrointestinal bleeding | IV      | IV     | IV         | Negative    | 4   | 2   |
| 11   | M   | 57  | Abdominal pain | II       | II\(_{a}\) | Iib        | Negative    | 0   | 0   |
| 12   | M   | 68  | Gastrointestinal bleeding | II     | II\(_{a}\) | Iia        | Negative    | 1   | 1   |

Age: age in years; IPI: international prognostic index; PIT: prognostic index for T-cell lymphoma.
Table 2. PET/CT features of 12 patients with MEITL on diagnosis and at relapse.

| Case | Status | FDG-avid lesions | Obstruction | Perforation | Histology proven sites |
|------|--------|------------------|-------------|-------------|------------------------|
|      |        | Stomach | Small bowel | Large bowel | Peritoneum | Regional LN | Distant sites |         |             |                                     |
| 1    | Dx     |        | 3.7         | –           | –          | –          | –           | PET/CT not available | Y   | N           | Small bowel                          |
|      | R1     | –       | 2–5         | 2–5         | 2.2        | –          | –           | –                | N   | N           | Small bowel                          |
|      | R2     | 7.2     | –           | –           | –          | –          | –           | Thigh: 4.9 Hypothalamus: 5.5 Left lung: 7.2 | Y   | N           | Thigh                                |
| 2    | Dx     | –       | 7.5–8.7     | –           | –          | –          | –           | PET/CT not available | N   | Y           | Small bowel, ascites                  |
|      | PD     | –       | 10.3        | –           | 8.0–12.9   | –          | –           | –                | N   | N           | Brain, ileum                          |
| 3    | Dx     | –       | 3.6–5.3     | –           | 3.6–5.3    | 2.0        | –           | PT LN, IM LN, SCF LN: 2–2.4, Diaphragm: 1.8 Pleura: 4.4 | N   | Y           | Small bowel, large bowel, omentum    |
|      | PD     | –       | –           | –           | –          | –          | –           | –                | –   | –           | –                                     |
| 4    | Dx     | –       | 7.7         | –           | –          | –          | –           | –                | –   | –           | –                                     |
| 5    | Dx     | –       | 3.6–5.3     | 1.5–2.9     | –          | –          | –           | SCF LN, PT LN, IM LN: 1.6–2.1 Breast: 1.1 Lung: 3.1 Spleen: 1.9 | N   | Y           | Small bowel, large bowel, omentum    |
| 6    | Dx     | –       | –           | –           | –          | –          | –           | –                | –   | –           | Colon                                 |
|      | PD     | –       | –           | –           | –          | –          | –           | –                | N   | N           | Colon                                 |
|      | R1     | –       | Appendix: 3.9 | –           | –          | –          | –           | –                | –   | –           | Colon                                 |
| 7    | Dx     | –       | –           | –           | –          | –          | –           | –                | N   | Y           | Small bowel, large bowel              |
|      | R1     | –       | –           | –           | –          | –          | –           | –                | –   | –           | –                                     |
|      | PD     | –       | Colitis: 6 | 0.9–2.5     | –          | –          | –           | Oesophagus: 2.4 Lung: 8.5 | N   | N           | Stomach                               |
| 8    | Dx     | –       | 7.7         | –           | –          | –          | –           | –                | N   | Y           | Duodenum                              |
| 9    | Dx     | –       | –           | –           | –          | –          | –           | –                | N   | N           | Small bowel                           |
| 10   | Dx     | 12.1–14.4 | –           | –           | –          | –          | –           | –                | N   | N           | Stomach                               |
| 11   | Dx     | –       | 4.5–5.0     | 4.3         | 1.8        | –          | –           | –                | N   | N           | Colon and LN                          |
| 12   | Dx     | –       | 4.5–5.0     | 4.3         | 1.8        | –          | –           | –                | N   | N           | Colon and LN                          |

Dx: at diagnosis; R1: first relapse; R2: second relapse; PD: progressive disease; SD: stable disease; LN: lymph node; SCF: supraclavicular fossa; PT: paratracheal; IM: internal mammary; *: post-operative at the small bowel; **: post-operative at the large bowel.
Positron emission tomography/computed tomography features of primary presentation in the small and large bowels

One case (patient 5) had concomitant involvement of the small and large bowels (both sites biopsy-proven). There was widespread involvement of multiple lymph nodes, pleura and lung.

Radiologic features in other cases on presentation

Two cases (patients 1 and 2) only had CT scans for staging. In patient 1, the disease was localized to the gastroduodenal junction. In patient 2, the lesion presented as an 8-cm circumscribed wall-off perforation in the abdomen communicating with the small bowel.

Treatment

Four patients received a methotrexate-containing regimen (methotrexate, ifosfamide, L-asparaginase, etoposide, dexamethasone) [4], whereas six patients received a cisplatin-containing regimen (cisplatin, ifosfamide, gemcitabine, L-asparaginase, etoposide, dexamethasone). Two patients received CHOP (cyclophosphamide, Adriamycin, vincristine, prednisolone).

Interim positron emission tomography/computed tomography

Nine patients had interim scan (after 2–3 cycles of treatment) (Table 3). Seven patients had metabolic...
complete response (mCR, DS: 1, \(N = 6\); DS: 3, \(N = 1\)), and two patients had disease persistence (DS: \(\geq 4\)). For the seven patients with interim mCR, two patients (cases 7 and 10) relapsed shortly afterwards and later succumbed to their illness; two patients (cases 4 and 6) had disease progression/relapse at end-of-treatment scan; one patient (case 8) died of complications during subsequent treatment; and only two patients (cases 11 and 12) maintained mCR at end-of-treatment scan. For the two patients showing disease persistence at interim, one patient achieved mCR at end-of-treatment scan (case 9), whereas the other patient (case 5) showed no improvement.

**Positron emission tomography/computed tomography features at progressive disease or relapse**

Five patients had PET/CT at PD or relapse. In four cases with primary small bowel tumour (Table 2), numerous sites were involved in three cases (patients 1, 2 and 7) including the thorax \((N = 3)\), breast \((N = 1)\), central nervous system (CNS) \((N = 1)\), distant lymph nodes \((N = 1)\), thigh \((N = 1)\) (Figure 4(A)) and liver and spleen \((N = 1)\) (Figure 3(B)). Interestingly, in one case with primary ileal involvement (patient 1), the lesion spread to the stomach at relapse (Figure 4(B)). In one case (patient 4), the relapse was restricted to the small bowel. In the remaining case (patient 6) with colon as the primary site, the CNS was remarkably the only site that was involved in disease progression (Figure 2(B)). It remained the only extra-intestinal site involved at relapse. Furthermore, although the primary colonic tumour was eumetabolic, metastatic lesions were hypermetabolic (appendix, \(\text{SUVmax} = 3.9\); sigmoid colon: \(\text{SUVmax} = 12.4\); basal ganglia: \(\text{SUVmax} = 4.4\); left frontal lobe: \(\text{SUVmax} = 4.9\)) (Figure 2(C)) (Table 2).

**Radiologic features in other cases at relapse**

Patient 10 had disease relapse in the CNS that progressed rapidly. He did not have a PET/CT done at relapse.

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**Table 3. PET/CT findings and outcome of 10 patients with MEITL.**

| Case | Status   | DS | \(\Delta \text{SUVmax} \) | Outcome       | Survival |
|------|----------|----|-----------------|---------------|----------|
| 1    | Relapse  | NA | 1               | NA\(^a\)      | Died of disease | 136 m    |
| 4    | Presentation | 1 | 5               | 100\%          | Died of disease | 11 m     |
| 5    | Presentation | 5 | 5               | NA\(^a\)      | Died of disease | 3 m      |
| 6    | Presentation | 1 | \(1^b\)          | NA\(^a\)      | Died of disease | 16 m     |
| 7    | Relapse   | 1  | NA\(^b\)        | 100\%          | Died of disease | 20 m     |
| 8    | Presentation | 5 | 5               | 0%             | Died of disease | 6 m      |
| 9    | Presentation | 4 | 1               | NA\(^a\)      | Died of complications\(^f\) | 14 m     |
| 10   | Presentation | 1 | NA\(^b\)        | 100\%          | Died of disease | 13 m     |
| 11   | Presentation | 1 | 1               | 100\%          | Alive            | 13 m     |
| 12   | Presentation | 3 | 1               | 22%            | Alive            | 13 m     |

\(\text{NA}:\) not available; \(\text{A}:\) presentation PET/CT scan not available; \(\text{B}:\) disease progression in CNS treated with radiotherapy, with mCR achieved at end-of-treatment scan; \(\text{C}:\) lesions eumetabolic on presentation; \(\text{D}:\) patient underwent autologous HSCT while in mCR; \(\text{E}:\) SUVmax not available on presentation; \(\text{F}:\) pancreatitis and upper gastrointestinal bleeding.

**Outcome and prognostic indicators**

The median survival of the cohort was 13 (1–136) months. Seven patients completed the intended therapy, with six of them achieving mCR (Table 3). Patients with mCR on completion of treatment had a median survival of 14 (13–136) months, which was apparently better than the patient who could not achieve mCR (patient 4, survival 11 months), although a formal statistical evaluation was not possible owing to the small number of cases.

**Discussion**

This study is to date the largest reported series of imaging features in MEITL patients. Our findings clearly distinguished this lymphoma from classical EATL, and gave important information on the clinical and biological characteristics of this new disease entity.

Classical EATL always arises from the small bowel, and involvement of the rest of the gastrointestinal tract has not been convincingly shown [9–11]. In MEITL, however, we showed with PET/CT that...
Involvement of the oesophagus, stomach and large bowel occurred in 50% of cases (Table 3), both on presentation and at relapse. On PET/CT, classical EATL occurs as hypermetabolic lesions with high SUVmax, against a background of diffuse FDG uptake of lower SUVmax deriving from the underlying coeliac disease [9,10]. In one series of four cases, classical EATL arising from coeliac disease had SUVmax of 6.4–8.0, which was significantly higher than the background SUVmax of 2.2–4.6 of the inflamed gut [9]. In our cases of MEITL, lesions appeared as discrete hypermetabolic lesions with no background activity, as enteropathy was not present. Although interpretation of the SUVmax of lesions depends on the values of the mediastinal blood pool or liver, the SUVmax values in MEITL were generally lower than those of aggressive B-cell lymphomas [13].

When classical EATL relapses, extra-intestinal sites are rarely if ever involved. In a total of 15 cases of classical EATL examined with PET/CT [9–11], only two cases had extra-intestinal involvement on relapse, presenting as mediastinal lymphadenopathy. Conversely, diverse extra-intestinal sites were involved during relapse in our cases.

Our results also provided novel observations in MEITL. It was not a gut-restricted lymphoma. On presentation and at relapse, many different anatomical sites were involved. Infiltration of thoracic structures (lung, pleura and diaphragm) occurred in 50% of our cases, which was surprisingly high when compared with that of merely 7% of thoracic involvement in aggressive diffuse large B-cell lymphoma (DLBCL) at any stage of illness [14]. During disease progression and relapse, the CNS was another site commonly involved. At a frequency of 25%, CNS involvement in our cases was again more common than that of approximately 7% in DLBCL [15]. The widespread involvement of extra-intestinal but non-nodal sites is reminiscent of the pattern observed in other aggressive extranodal T-cell lymphomas.

In conclusion, PET/CT scan findings have shown that MEITL is distinctly different from classical EATL in many aspects (Table 4). These observations are consistent with recent genetic studies that showed different mutational profiles in MEITL and classical EATL [15]. Finally, the high frequency of extra-intestinal involvement in MEITL, particularly the CNS, suggests that high-dose chemotherapy may be needed to improve treatment outcome.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Isaacson PG, Chott A, Ott G, et al. Enteropathy-associated T-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumours of the haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC; 2008. p. 89–291.
[2] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–2390.
[3] Chan JK, Chan AC, Cheuk W, et al. Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent γδ T-cell receptor expression. Am J Surg Pathol. 2011;35(10):1557–1569.
[4] Tse E, Gill H, Loong F, et al. Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia lymphoma study group. Am J Hematol. 2012;87(7):663–668.
[5] Tan SY, Chuang SS, Tang T, et al. Type II EATL (epitheliotropic intestinal T-cell lymphoma): a neoplasm of intraepithelial T-cells with predominant CD8αα phenotype. Leukemia. 2013;27(8):1688–1696.

| Table 4. Differences in PET/CT features between MEITL and classical EATL. |
|-------------------|-----------------|-----------------|-----------------------------|
| PET/CT features   | MEITL           | EATL            | Remarks                     |
| **On presentation** |                 |                 |                             |
| Primary site      | Any part of the gastrointestinal tract | Exclusively small bowel | EATL is restricted to site of coeliac disease (small bowel) |
| FDG-avidity       | May be eumetabolic in colonic lesions | Hypermetabolic | MEITL might be eumetabolic as no underlying enteropathy |
| **Extra-intestinal sites** | Regional and distant lymph nodes, thorax | Uncommon | MEITL has a propensity to metastasize regionally and systemically |
| Un-involved gut   | No increase in FDG-avidity | Mildly increased FDG-avidity | EATL arises from a background of FDG-avid coeliac disease |
| **At disease progression or relapse** |                 |                 |                             |
| Gastrointestinal tract | Any part of the gastrointestinal tract | Predominantly in the small bowel | EATL is a small bowel-restricted T-cell lymphoma |
| Thoracic structures | Involved in 50% of cases | Exceptionally rare | MEITL is a systemic T-cell lymphoma |
| CNS               | Involved in 25% of cases | Exceptionally rare |                             |
| Other distant sites | Breast, liver, spleen, limbs | Not reported before |                             |
| Interim scan      | Uncertain prognostic value | Not reported before |                             |
| End-of-treatment scan | mCR might indicate better survival | Not reported before |                             |

FDG: 18F-deoxyglucose; mCR: metabolic complete response.
[6] Tan SY, Ooi AS, Ang MK, et al. Nuclear expression of MATK is a novel marker of type II enteropathy-associated T-cell lymphoma. Leukemia. 2011;25(3):555–557.

[7] Swerdlow SH, Jaffe ES, Brousset P, et al. International lymphoma study group. Cytotoxic T-cell and NK-cell lymphomas: current questions and controversies. Am J Surg Pathol. 2014;38(10):e60–e71.

[8] Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol. 2014;32(27):3048–3058.

[9] Hoffmann M, Vogelsang H, Kletter K, et al. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for assessment of enteropathy-type T cell lymphoma. Gut. 2003;52(3):347–351.

[10] Hadithi M, Mallant M, Oudejans J, et al. 18F-FDG PET versus CT for the detection of enteropathy-associated T-cell lymphoma in refractory celiac disease. J Nucl Med. 2006;47(10):1622–1627.

[11] Casulo C, Schöder H, Feeney J, et al. 18F-fluorodeoxyglucose positron emission tomography in the staging and prognosis of T cell lymphoma. Leuk Lymphoma. 2013;54(10):2163–2167.

[12] Khong PL, Huang B, Lee EY, et al. Midtreatment 18F-FDG PET/CT scan for early response assessment of immune therapy in natural killer/T-cell lymphoma: a prospective study from a single center. J Nucl Med. 2014;55(6):911–916.

[13] Chan WK, Au WY, Wong CY, et al. Metabolic activity measured by F-18 FDG PET in natural killer-cell lymphoma compared to aggressive B- and T-cell lymphomas. Clin Nucl Med. 2010;35(8):571–575.

[14] Mian M, Wasle I, Gritsch S, et al. B cell lymphoma with lung involvement: what is it about? Acta Haematol. 2015;133(2):221–225.

[15] Villa D, Connors JM, Shenkier TN, et al. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. Ann Oncol. 2010;21(5):1046–1052.