1. GENERAL INFORMATION

1.1 Definition

Enteropathy-associated T-cell lymphoma (EATL) is an intestinal tumour of intraepithelial T lymphocytes, usually presenting as a neoplasm composed of large lymphoid cells and often associated with necrosis and an inflammatory background, including a large number of histiocytes and eosinophils. The adjacent small intestinal mucosa shows villous atrophy, crypt hyperplasia, increased lamina propria lymphocytes and plasma cells, and intraepithelial lymphocytosis. In 10-20% of cases, the lymphoma is composed of monomorphic medium-sized cells with no inflammatory background and rare necrosis (type II EATL). Intestinal intraepithelial alpha-beta T cells, in various stages of transformation, have been postulated as the normal-cell counterpart for EATL. This seems to be supported by immunophenotypic and genotypic data, as well as by the cytotoxic differentiation observed in the neoplastic cells of almost all cases of EATL (Daum 1997).

1.2 Incidence and Risk factors

EATL represents 10% to 25% of all primary lymphomas of the small bowel, and is the most common neoplastic complication of coeliac disease. EATL is uncommon in most parts of the world, but is seen with greater frequency in those areas with a high prevalence of coeliac disease, in particular Northern Europe. Ten percent of patients affected by coeliac disease will develop an intestinal lymphoma, and 65% of them will have T-immunophenotype. The interval between diagnosis of coeliac disease and development of lymphoma is extremely variable, oscillating from 2 months to more than 5 years (Ilyas 1995). Human leukocyte antigen (HLA) genotyping shows that patients with EATL have the coeliac disease-associated DQA1*0501, DBQ1*0201 phenotype, and additional HLA-DR/DQ alleles may increase the risk of lymphoma (Wright 1995). In some cases of refractory coeliac disease (RCD), the intraepithelial lymphocytes (IEL) are phenotypically aberrant showing down-regulation of CD8 similar to the IEL in mucosa adjacent to EATL. These cases also show monoclonal T-cell rearrangement of the IEL similar to the clonal rearrangements that may be found in the

enteropathic mucosa adjacent to EATL (Bagdi 1999), suggesting that the immunophenotypically aberrant IEL constitute a neoplastic population. In those patients with RCD who subsequently develop EATL, the IEL share the same monoclonal TCRγ as the subsequent T-cell lymphoma (Ashton-Key 1997; Cellier 2000; Cellier 1998; Daum 2005). Furthermore, in cases of RCD the IEL carry gains of chromosome 1q in common with EATL (Verkarre 2003). Therefore, RCD in which the IEL show these immunophenotypic and genetic features can be considered as examples of intraepithelial T-cell lymphoma or, alternatively, EATL in situ. The monomorphic form of EATL may also be preceded by RCD in which the immunophenotype of the IEL is similar to that of the neoplastic cells in the subsequent lymphoma, namely CD8+ and CD56+. This variant occurs sporadically, without risk factors for coeliac disease, and appears to have a broader geographic distribution. In patients without a prior diagnosis of coeliac disease, EATL is a very rare disorder, and in these cases diagnosis is often difficult and delayed. Another condition associated with EATL is ulcerative jejunitis. Small bowel is the most frequent extranodal site of presentation among NHLs developing in solid-organ graft recipients who did not receive cyclosporine (Thomas 1991), especially renal graft recipients. In these patients, in contrast to cases that occur in individuals treated with cyclosporine, the time interval between grafting and lymphoma development exceeds12 months (Penn 1987).

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2. PATHOLOGY AND BIOLOGY

2.1 Morphology

EATL more often occurs in the jejunum or ileum in the form of one or more ulcerating mucosal lesions that invade the wall of the intestine and frequently cause perforation. This is in contrast to what is seen in B-cell lymphomas, which tend to affect the distal or terminal ileum, by producing annular infiltration or polypoid masses (Domizio 1993; Quintanilla-Martinez 1997). Classical EATL shows a wide range of cytological appearances (Isaacson 1994; Wright 1997). Most commonly, neoplastic cells are rather monotonous, medium-large sized with round or indented nuclei, prominent nucleoli and an evident rim of pale staining cytoplasm. Less frequently, they are pleomorphic, mimicking anaplastic large cell lymphoma. An inflammatory background is usually present: it consists of histiocytes and eosinophils that at times are so numerous as to obscure the lymphomatous population. Infiltration of the epithelium of individual crypts is recorded in many cases. The intestinal mucosa adjacent to the neoplasm frequently shows enteropathy with villous atrophy, crypt hyperplasia, increased lamina propria lymphocytes and plasma cells and intraepithelial lymphocytosis (Chott 1998). In type II EATL, the neoplastic cells are homogeneously medium-sized with darkly stained nuclei and a moderate rim of pale cytoplasm. The adjacent mucosa does also show villous atrophy and crypt hyperplasia with striking intraepithelial lymphocytosis. However, there is no inflammatory background and n ecrosis is less evident than in classical EATL.

2.2 Immunophenotype

In EATL, tumour cells are CD3+,CD5-, CD7+, CD8-/+, CD4-, CD103+, TCRβ+/-, and contain cytotoxic molecules (TIA-1, granzyme a, granzyme M and perforin). In almost all cases, a

varying proportion of tumour cells express CD30. The intraepithelial lymphocytes in the adjacent enteropathic mucosa may show the same phenotype as lymphomatous elements. Type II EATL has a distinctive immunophenotype. The tumour cells are CD3+, CD4-, CD8+, CD56+ and TCRß+.

2.3 Genetic features

TCRβ and γ genes are clonally rearranged in all morphological variants. Patients with EATL usually carry the HLADQA1*0501, DQB1*0201 genotype that is seen in more than 90% of patients with coeliac disease (Howell 1995). About 70% of EATL cases harbour complex segmental amplifications of the 9q31.3-qter chromosome region or, alternatively, show del16q12.1, which is prevalent in both morphological variants of EATL. Chromosomes gains in 1q and 5q are frequent in classical EATL, while 8q24 (myc) amplifications are more common in the monomorphic variant (Deleeuw 2007; Zettl 2002; Zettl 2007).

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3. DIAGNOSIS

3.1 Clinical presentations

EATL usually occurs in adults, often with a history of gluten-sensitive enteropathy, but occasionally as the initial event in a patient found to have the typical histologic features of sprue in the resected intestine. Less commonly, it arises in patients without evidence of enteropathy; in these cases, diagnosis is difficult and delayed due to the non-specific nature of the symptoms and a very low index of clinical suspicion. Patients generally present with abdominal pain, often associated with jejunal perforation, weight loss, diarrhoea, or bowel obstruction. Since obstruction and perforation are common, many cases are diagnosed at laparotomy. EATL is characterized by multifocal presentation in 10% to 25% of cases (Levine 1997). Small-bowel lymphoma is more common than large-bowel or rectal lymphomas. The higher frequency of intestinal perforation at diagnosis may account for the high perioperative complication rate in this lymphoma. A relationship between EATL and eosinophilia has been seldom reported (Hovenga 2003). Neurologic symptoms are reported in approximately 6% of adults with celiac disease; cerebellar ataxia is the most frequent symptom reported. Generally, any extra-intestinal manifestation of a T-cell NHL in a patient with celiac disease should be considered as a possible manifestation of a cryptogenic EATL, even if the enteropathy is clinically asymptomatic (Gobbi 2003).

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4. STAGING

4.1 Staging procedures

Complete staging work-up for EATL includes an accurate physical examination (Waldeyer's ring involvement should be excluded), complete haematological and biochemical exams,

total-body computerized tomography, gastrointestinal tract examination, and bone marrow aspirate and biopsy. Unlike primary gastric lymphoma, where a surgical approach is progressively being replaced by conservative management, most patients with EATL still undergo exploratory laparotomy for diagnosis and staging. In patients with EATL who have not had a surgical exploration, barium studies of the small and large intestine and pancolonscopy with biopsy sampling of all macroscopically evident lesions should be performed because of the frequent multifocal nature of this malignancy. Abdominal staging, with evaluation of potential hepatic or splenic involvement in EATL is usually performed during exploratory laparotomy. In patients managed with a conservative approach, abdominal staging should follow the general principles as for all NHL. 18F-FDG PET is able to discriminate between refractory celiac disease and EATL; in 38 examined patients, PET revealed sites affected by EATL as confirmed on biopsy in all patients, whereas CT scan was false negative in one patient. False-positive results in PET may be due to inflammation in refractory celiac disease (Hadithi 2006).

4.2 Staging system

The Ann Arbor staging system (Carbone 1971), currently used for the majority of non-Hodgkin's lymphomas, has been considered unsatisfactory for EATL. Several alternative staging systems have been used for this malignancy (Musshoff 1977; Blackledge 1979; Rohatiner 1994). An International Workshop of 1994 recommended the following classification (Rohatiner 1994):
Stage I: lymphoma confined to the gastrointestinal tract. Single primary site or multiple noncontiguous lesions.
Stage II: lymphoma extending in abdominal lymph nodes from primary gastrointestinal site.
Stage II1: involvement of local (paragastric or paraintestinal) lymph nodes
Stage II2: involvement of distant (mesenteric, para-aortic, paracaval, pelvic, inguinal) lymph nodes
Stage IIE: penetration of serosa to involve adjacent organs or tissues Stage IV: diffuse or disseminated involvement of one or more extralymphatic organs, or a gastrointestinal tract lesion with supradiaphragmatic nodal involvement.
Patients should be divided in two subsets according to the presence (A) or absence (B) of systemic symptoms. Fever of no evident cause, night sweats and weight loss of more than 10% of body weight are considered systemic symptoms. These symptoms must be meticulously evaluated because they are frequently due to causes other than intestinal lymphoma. Several EATL patients have remarkable weight loss due to severe associated enteropathy; fever can be secondary to a concomitant but not obvious sepsis in an immunocompromised individual. The presence of bulky mass, such as a lesion of 10 cm or more in the longest diameter, is designated as "X".

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5. PROGNOSIS

5.1 Natural history

EATL is an aggressive malignancy which, if untreated, leads invariably to death due to multifocal intestinal perforation caused by refractory malignant ulcers. Since its association with gluten-sensitive enteropathy, most patients with EATL are extremely compromised from an immunological and nutritional point of view. Most patients with EATL are managed with a surgical approach as primary strategy. Even if surgical operation is not a curative treatment, debulking and resection of masses with high-risk of perforation or occlusion are frequently

indicated in these patients. The higher frequency of intestinal perforation at diagnosis may account for the high perioperative complication rate in this lymphoma. The prognosis of EATL is very poor, as compared with B-cell intestinal lymphomas (Domizio 1993). EATL usually shows low chemosensitivity, rapid tumour growth and a tendency to dissemination. Moreover, the higher incidence of severe postsurgical complications and the poor nutritional and immunological conditions of these patients lead to progressive clinical deterioration, preventing the use of adequate and opportune treatment.

5.2 Prognostic factors

Considering the heterogeneity and the small number of patients reported in any single series, reliable prognostic factors for EATL have not been established. Actually, the majority of EATL patients have been reported as part of large series of patients with different primary gastrointestinal lymphomas. These series were usually managed heterogeneously and included patients with all stages of disease. Stage is the main prognostic factor in EATL, with a 5-year cause-specific survival higher than 60% for patients with limited disease and 25% for those with advanced EATL (Chott 1992; D'Amore 1994). In the largest series of gastrointestinal lymphoma, bulky lesion, stage, histology, immunophenotype, B symptoms, and LDH ratio have been reported as the main prognostic indicators (Chott 1992; D'Amore 1994 ; Liang 1991; Morton 1993). In a large series of intestinal lymphomas, perforation, high-grade histology, multiple tumours and advanced stage have been identified as the main adverse prognostic features (Domizio 1993).

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6. TREATMENT

6.1 Treatment of limited disease (Stage I-II)

A standard treatment for patients with stage I-II EATL has not been established, and overall reported results with varied modalities are unsatisfactory. Combined treatment with primary systemic conventional-dose anthracycline-containing chemotherapy which may or may not be followed by radiation therapy, is suitable for individual clinical use on a type 3 level of evidence (D'Amore 1994; Liang 1991; Morton 1993). The role of surgery is limited to debulking or resection of masses with high-risk of obstruction or perforation and is suitable for individual clinical use on a type R basis. The use of chemotherapy in cases of incomplete resection is associated with a 5% - 15% incidence of intestinal perforation and other complications. A better prognosis in patients who have undergone macroscopically complete resection, as compared with those who have residual disease, has been reported, but these data come from retrospective small series and cannot be considered definitive (Stewart 1991; Zinzani 1997; Shih 1994). Patients who have undergone complete resection as primary treatment should receive adjuvant anthracycline-based chemotherapy. Radiation therapy is usually indicated in patients presenting with bulky disease, rectal lymphoma or incomplete resection. Involved-field delivering 35 Gy in 1.5 to 2-Gy daily fractions, 5 fractions a week is suitable for individual clinical use on a type R basis.
Despite some successfully treated case reports (Honemann 2005), standard anti-lymphoma chemotherapy combinations have minimal utility in patients with EATL. Some studies have reported autologous stem cells transplantation as an effective therapeutic option. A study demonstrated good results using two cycles of IVE (ifosphamide, etoposide, epirubucin) followed by two cycles of high dose methotrexate (3 g/mq) and BEAM autograft (carmustine, etoposide, cytarabine, melphalan); four patients remained alive and disease-free after 2-4 years from treatment, while two patients relapsed. Considering the poor prognosis of these patients, this regimen seems very promising (Bishton 2007). Chemotherapy supported by

autologous bone marrow transplantation may also prevent EATL development in patients with RCD (Meijer 2004).

6.2 Treatment of advanced disease (Stage IV)

A standard therapeutic option for patients with stage IV disease is conventional-dose anthracycline-containing chemotherapy which may or may not be followed by radiotherapy on a type R basis. The role of surgery is limited to debulking or resection of masses with high-risk of occlusion or perforation. Primary debulking resection and anthracycline-based chemotherapy, with or without subsequent radiotherapy, have been associated with a 5-yr survival of 25% (Domizio 1993; D'Amore 1994; Morton 1993).

6.3 Treatment of relapsed or refractory disease

A standard therapeutic option for patients with relapsed or refractory disease has not been established. High-dose chemotherapy supported by autologous stem cell transplantation should be taken into account in these patients considering the aggressive behaviour of relapsed T-cell lymphomas and the lack of valid therapeutic alternatives. The rationale for using this strategy is immunoablation using high-dose chemotherapy, with subsequent regeneration of naïve T-lymphocytes derived from reinfused haematopoietic progenitor cells. Moreover, the use of autologous stem cell transplantation allows the administration of high-dose chemotherapy resulting in a prompt remission in these therapy-refractory patients (Al-Toma 2007). However, the worldwide experience is very limited, and this remains an investigational option (Jaffe 1999). Special attention should be paid to eligibility criteria for intensive therapeutic strategies, considering the poor performance status of these patients at relapse. In some cases, whole-abdomen irradiation with 20 to 25 Gy delivered in 1- to 1.25-Gy daily fractions may be indicated for palliative treatment (Crump 1999).

References

Al-Toma A, Mulder CJ. Review article: Stem cell transplantation for the treatment of gastrointestinal diseases--current applications and future perspectives. Aliment Pharmacol Ther 2007;26 Suppl 2:77-89.:77-89 [Medline]

Ashton-Key M, Diss TC, Pan L, Du MQ, Isaacson PG. Molecular analysis of T-cell clonality in ulcerative jejunitis and enteropathy-associated T-cell lymphoma. Am J Pathol 1997;151:493-498 [Medline]

Bagdi E, Diss TC, Munson P, Isaacson PG. Mucosal intra-epithelial lymphocytes in enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and refractory celiac disease constitute a neoplastic population. Blood 1999;94:260-264 [Medline]

Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. Br J Haematol 2007;136:111-113 [Medline]

Blackledge G, Bush H, Dodge OG, Crowther D. A study of gastro-intestinal lymphoma. Clin Oncol 1979;5:209-219 [Medline]

Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1861 [Medline]

Cellier C, Delabesse E, Helmer C, et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. Lancet 2000;356:203-208 [Medline]

Cellier C, Patey N, Mauvieux L, et al. Abnormal intestinal intraepithelial lymphocytes in

refractory sprue. Gastroenterology 1998;114:471-481 [Medline]

Chott A, Dragosics B, Radaszkiewicz T. Peripheral T-cell lymphomas of the intestine. Am J Pathol 1992;141:1361-1371 [Medline]

Chott A, Haedicke W, Mosberger I, et al. Most CD56+ Intestinal Lymphomas Are CD8+CD5- T-Cell Lymphomas of Monomorphic Small to Medium Size Histology. Am J Pathol 1998;153:1483-1490 [Medline]

Crump M, Gospodarowicz M, Shepherd FA. Lymphoma of the gastrointestinal tract. Semin Oncol 1999;26:324-337 [Medline]

D'Amore F, Brincker H, Gronbaek K, et al. Non-Hodgkin's lymphoma of the gastrointestinal tract: a population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. Danish Lymphoma Study Group. J Clin Oncol 1994;12:1673-1684 [Medline]

Daum S, Cellier C, Mulder CJ. Refractory coeliac disease. Best Pract Res Clin Gastroenterol 2005;19:413-424 [Medline]

Daum S, Foss HD, Anagnostopoulos I, et al. Expression of cytotoxic molecules in intestinal T-cell lymphomas. The German Study Group on Intestinal Non-Hodgkin Lymphoma. J Pathol 1997;182:311-317 [Medline]

Deleeuw RJ, Zettl A, Klinker E, et al. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology 2007;132:1902-1911 [Medline]

Domizio P, Owen RA, Shepherd NA, Talbot IC, Norton AJ. Primary lymphoma of the small intestine. A clinicopathological study of 119 cases. Am J Surg Pathol 1993;17:429-442 [Medline]

Gobbi C, Buess M, Probst A, et al. Enteropathy-associated T-cell lymphoma with initial manifestation in the CNS. Neurology 2003;60:1718-1719 [Medline]

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;47:1622-1627 [Medline]

Honemann D, Prince HM, Hicks RJ, Seymour JF. Enteropathy-associated T-cell lymphoma without a prior diagnosis of coeliac disease: diagnostic dilemmas and management options. Ann Hematol 2005;84:118-121 [Medline]

Hovenga S, de GH, Joosten P, et al. Enteropathy-associated T-cell lymphoma presenting with eosinophilia. Neth J Med 2003;61:25-27 [Medline]

Howell WM, Leung ST, Jones DB, et al. HLA-DRB, -DQA, and -DQB polymorphism in celiac disease and enteropathy-associated T-cell lymphoma. Common features and additional risk

factors for malignancy. Hum Immunol 1995;43:29-37 [Medline]

Ilyas M, Niedobitek G, Agathanggelou A, et al. Non-Hodgkin's lymphoma, coeliac disease, and Epstein-Barr virus: a study of 13 cases of enteropathy-associated T- and B-cell lymphoma. J Pathol 1995;177:115-122 [Medline]

Isaacson PG, Norton AJ, Editors. Extranodal Lymphomas. 1st ed. Edinburgh, Scotland: Churchill Livingstone.1994

Jaffe ES, Krenacs L, Kumar S, Kingma DW, Raffeld M. Extranodal peripheral T-cell and NK-cell neoplasms. Am J Clin Pathol 1999;111:S46-S55 [Medline]

Levine MS, Rubesin SE, Pantongrag-Brown L, Buck JL, Herlinger H. Non-Hodgkin's lymphoma of the gastrointestinal tract: radiographic findings. AJR Am J Roentgenol 1997;168:165-172 [Medline]

Liang R, Chiu E, Chan TK, Todd D, Loke SL. Direct comparison of peripheral T-cell lymphomas with their B-cell counterpart. Acta Haematol 1991;85:179-183 [Medline]

Meijer JW, Mulder CJ, Goerres MG, Boot H, Schweizer JJ. Coeliac disease and (extra)intestinal T-cell lymphomas: definition, diagnosis and treatment. Scand J Gastroenterol Suppl 2004;78-84 [Medline]

Morton JE, Leyland MJ, Vaughan HG, et al. Primary gastrointestinal non-Hodgkin's lymphoma: a review of 175 British National Lymphoma Investigation cases. Br J Cancer 1993;67:776-782 [Medline]

Musshoff K. [Clinical staging classification of non-Hodgkin's lymphomas (author's transl)]. Strahlentherapie 1977;153:218-221 [Medline]

Penn I. Cancers following cyclosporine therapy. Transplantation 1987;43:32-35 [Medline]

Quintanilla-Martinez L, Lome-Maldonado C, Ott G, et al. Primary non-Hodgkin's lymphoma of the intestine: high prevalence of Epstein-Barr virus in Mexican lymphomas as compared with European cases. Blood 1997;89:644-651 [Medline]

Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol 1994;5:397-400 [Medline]

Shih LY, Liaw SJ, Dunn P, Kuo TT. Primary small-intestinal lymphomas in Taiwan: immunoproliferative small-intestinal disease and nonimmunoproliferative small-intestinal disease. J Clin Oncol 1994;12:1375-1382 [Medline]

Stewart AK, Shepherd FA, Goss PE, et al. Gastrointestinal non-Hodgkin's lymphoma. Leuk Lymphoma 1991;4:167-176

Thomas JA, Allday MJ, Crawford DH. Epstein-Barr virus-associated lymphoproliferative disorders in immunocompromised individuals. Adv Cancer Res 1991;57:329-80.:329-380 [Medline]

Verkarre V, Romana SP, Cellier C, et al. Recurrent partial trisomy 1q22-q44 in clonal intraepithelial lymphocytes in refractory celiac sprue. Gastroenterology 2003;125:40-46 [Medline]

Wright DH. Enteropathy associated T cell lymphoma. Cancer Surv 1997;30:249-61.:249-261 [Medline]

Wright DH. The major complications of coeliac disease. Baillieres Clin Gastroenterol 1995;9:351-369 [Medline]

Zettl A, Ott G, Makulik A, et al. Chromosomal gains at 9q characterize enteropathy-type T-cell lymphoma. Am J Pathol 2002;161:1635-1645 [Medline]

Zettl A, Rudiger T, Muller-Hermelink HK. [Enteropathy type T-cell lymphomas: pathology and pathogenesis]. Pathologe 2007;28:59-64 [Medline]

Zinzani PL, Magagnoli M, Pagliani G, et al. Primary intestinal lymphoma: clinical and therapeutic features of 32 patients. Haematologica 1997;82:305-308 [Medline]

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