Primary duodenal follicular lymphoma : 6-years complete remission after combined radio-immunotherapy

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Abstract

Primary gastrointestinal lymphoma (PGL) is known to account for 40% of all extranodal non-Hodgkin's lymphomas (NHLs) and between 4% to 12% of all NHLs. The small intestine is the site of presentation in 20-30% of cases, with the terminal ileum usually involved. Duodenal localizations have always been thought to be rare, but are presently growing in incidence. We herein report on a case of Stage IV primary duodenal FCL, located to the second portion of the duodenum with concomitant minimal bone marrow involvement. The patient was frontline approached with a conservative combined modality treatment consisting of 4 weekly infusions of the chimeric human-murine IgG1 mono-clonal antibody against the B-cell surface antigen CD-20, Rituximab (375 mg/m2) and consolidation 3D conformal external beam radiotherapy up to a total dose of 36 Gy given into 20 fractions to the involved duodenal portion. Six years after treatment has been completed, the patient is free from disease with no treatment-related toxicity. (Acta gastroenterol. belg., **2011**, 74, **337-342**).

Key words : radiotherapy, follicular, duodenal, lymphoma, rituximab.

Introduction

Primary gastrointestinal lymphoma (PGL) is known to account for 1 to 4% of all gastro-intestinal malignancies (1). Moreover, the gastro-intestinal tract as a site of origin for non-Hodgkin's lymphomas (NHLs) includes from 4 to 12% of them and 40% of all extranodal NHLs (2). While the stomach is the most common site of involvement, accounting for approximately 50-60% of all cases, the small intestine is the primary location in 20-30%. It often occurs within the terminal ileum, whereas duodenal localizations have always been thought to be rare, but are presently growing in incidence (2-4). Concerning histology, high-grade diffuse large B-cell lymphoma and mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) represent the vast majority of PGLs ; follicular cell lymphoma (FCL) accounts for only 1-7% of them (4-7). Primary FCL of the duodenum is a rare disease that has been recently recognized as a distinct clinico-pathologic entity. A few studies of duodenal FCL have shown that it has features similar to those of conventional nodal follicular lymphoma with an indolent clinical course and immuno-histological features undistinguishable from nodal follicular lymphoma (8). We herein report on a case of Stage IV primary duodenal FCL, located to the second portion of the duodenum with concomitant minimal bone marrow involvement. The treatment approach consisted of combined immuno-radiation which achieved a long lasting complete remission.

Case report

In 2003, a 42 aged healthy women was referred to our institutional hospital, due to the recent appearance of epigastric discomfort usually worsening shortly after food intake, accompanied by nausea sensation and sporadic vomiting. Patient's previous medical history was silent, apart from a minimal change in bowel habits and a slight weight loss during the last four months. Physical examination could not reveal any remarkable finding, with no superficial lymphadenopathy detectable. Moreover no hepato-splenomegaly or cutaneous lesions could be highlighted. Complete blood count and serum biochemistry were performed, but all findings were within normal limits. However, serum anti-Helicobacter Pylori antibodies were demonstrated as positive (65 U/ml). Thereby, to confirm clinical suspicious, an upper gastrointestinal endoscopy was performed, with the evidence of a duodenal granular flat elevated mucosal lesion, irregularly shaped and composed of whitish, coarsely lumped, polypoid raised granules (Fig. 1a). The patient subsequently underwent a punch biopsy of the lesion showing the presence of neoplastic follicles composed predominantly of small-to-medium-sized cleaved cells (centrocytes) with scattered small round lymphocytes. Immunostaining showed that atypical cells were positive for antibodies directed towards the B-lineage antigens such as L-26, CD 10, CD 20, Cd79a, CD 75 and BCL-2, (intensely positive in the nodule center) and negative for CD5 and CD3, CD23 and cyclin D1. A diagnosis of lymphoma was made and it was classified according to the Revised European-American Lymphoma Classification as a follicle center lymphoma,

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follicular, grade 1. Moreover, no evidence of Helicobacter Pylori could be detected after gastrointestinal endoscopy.

A complete staging work-up was performed. Endoscopic ultrasonography (EUS) demonstrated a substantial thickening of the mucosal and submucosal layers of the 2nd portion of duodenal wall with the synchronous evidence of multiple hypoechoic granules. A complete enteroscopy procedure was performed with the ingestion of a wireless capsule in the shape of videocapsule endoscopy (VCE). Lesions were uniquely located within the duodenum. A computed tomography scans of the chest, abdomen and pelvis failed to show any lymph node enlargement. Bone marrow aspiration showed a minimal invasion by small sized cleaved cells. The tumour was staged as IV due to bone marrow involvement (according to Musshoff's modification of the Ann Arbor classification) (9). The patient was first approached with immunotherapy including a weekly infusion of the chimeric human-murine IgG1 monoclonal antibody against the B-cell surface antigen CD-20, Rituximab (375 mg/m2). After completion of immunotherapy, an upper gastrointestinal endoscopy was repeated in order to evaluate FCL response to rituximab. The examination demonstrated a partial response of the duodenal lesion, diminishing in size and thickening (Fig. 1b). In order to consolidate rituximab results, the patient underwent a full course of external beam radiation therapy delivered with a three-dimensional conformal filed arrangement (Fig. 2). The conventionally fractionated total dose was up to 36 Gy given in 20 fractions. Localization of the lesion was facilitated by the placement of a metallic clip in the peri-lesional region during the endoscopic restaging procedure (Fig. 1c). No acute toxicity could be recorded. One month after RT had been completed, a re-evaluation endoscopy showed a complete disease remission with the total disappearance of the duodenal lesion (Fig. 1d). The first bone marrow aspiration, performed at six months, showed the persistence of minimal residual disease (MRD) with nested Polymerase Chain Reaction (PCR) for Bcl-2/Ig-H translocation. At one year, a second biopsy demonstrated the achievement of a molecular remission (MR) status. Six years after treatment the patient is still in complete maintained MR. No treatment-related toxicity has yet been recorded up to last follow-up examination.

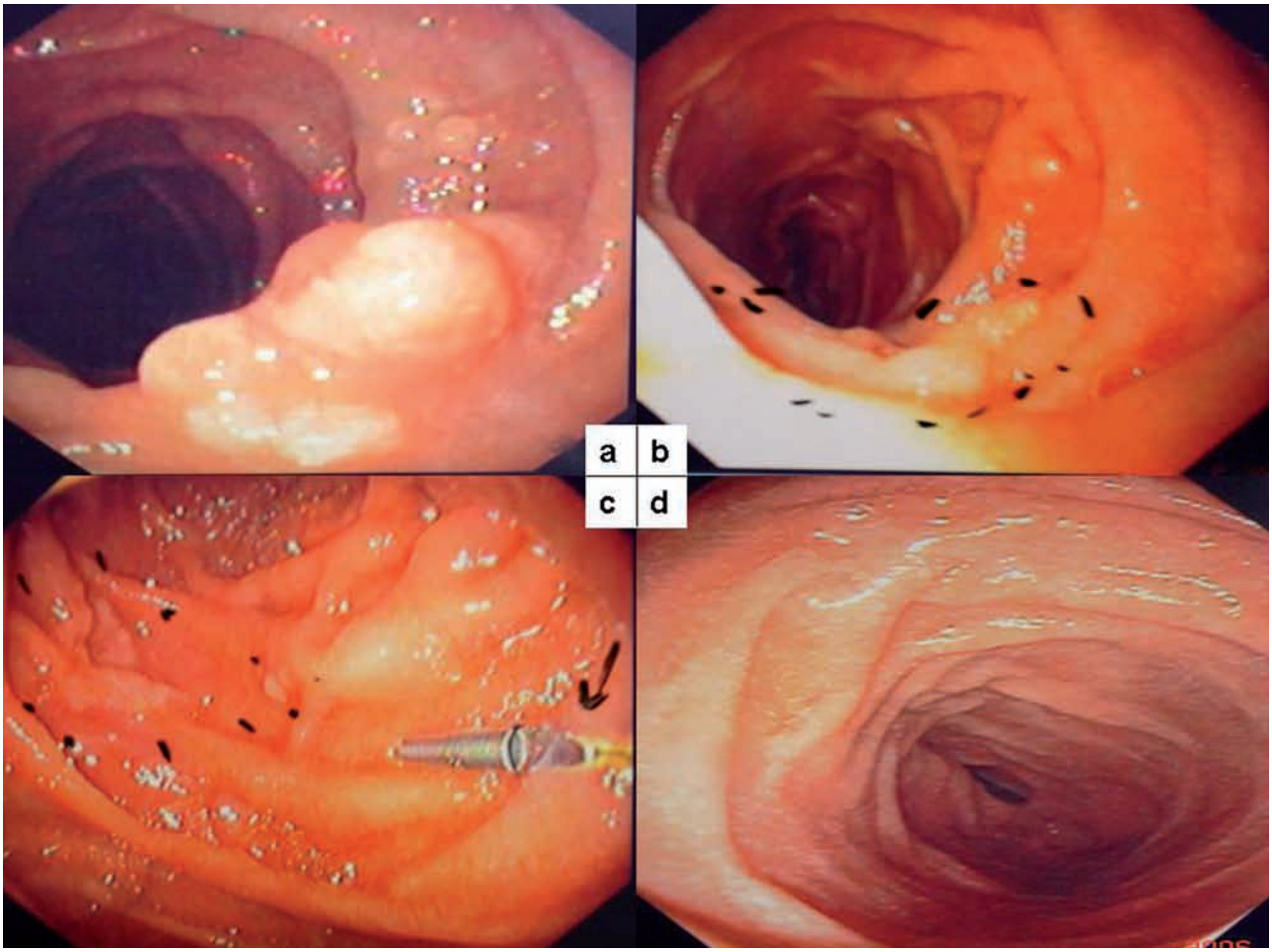

Fig. 1. — Granular flat elevated mucosal vegetation of the duodenum at diagnostic upper gastrointestinal endoscopy (a) ; partial remission of the macroscopic lesion after 4 cycles of Rituximab (b) ; metallic clip placed during restaging endoscopy (c) ; complete remission after 36 Gy external beam radiation therapy (d).

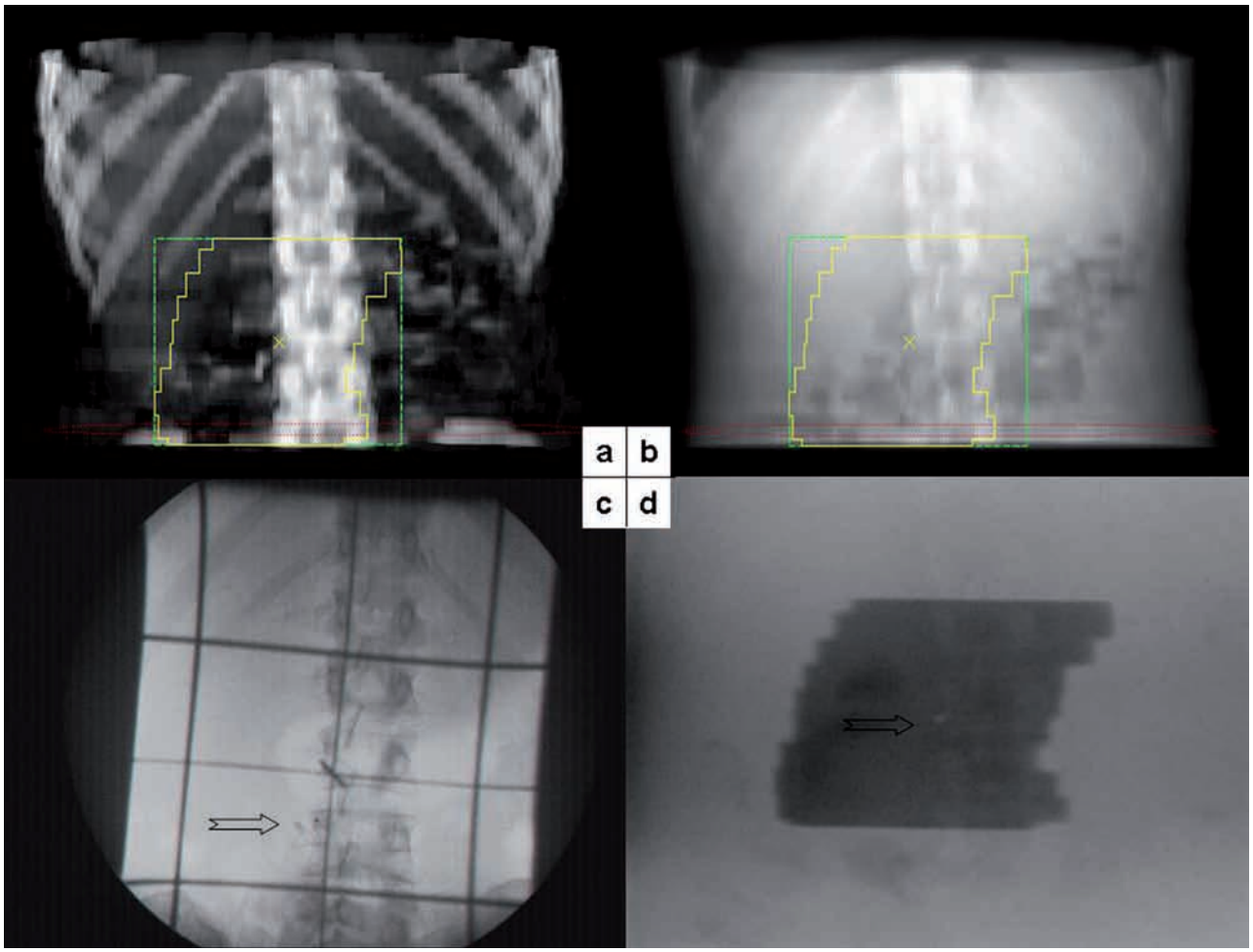

Fig. 2. — Antero-posterior view on digitally reconstructed radiographies (a,b) ; evidence of metallic clip (arrow) during simulation fluoroscopy (c) ; anterior electronic portal image with radio-opaque clip (arrow) acquired during treatment (d).

Discussion

Early reports have stated that duodenal lymphomas are a rare clinicopathological entity, since gastro-intestinal tract (GI) lymphomas mainly involve the stomach and the colorectum. However follicular cell histology is a frequent finding among them (3,10). LeBrun *et al.* described 31 cases of follicular cell lymphomas (FCL) of the GI tract in which lesions were predominantly located within the small intestine (55%), showing a peculiar predilection for the terminal ileum. No mention was made about the exact number of duodenal cases (8). More recently, Yoshino *et al.* reported a high incidence of follicular duodenal lymphoma (4). In their series, 8 out of 222 cases (3.6%) arose from the GI mucosa. Among them, 5 out of 8 cases belonged to the duodenum. When these data have been updated, 52 extranodal follicular lymphomas out of 550 (10%) were described ; among them 40 cases were located within the duodenum. The authors observed that this finding might be due to the usual exploration of duodenal tract during routine endoscopies which is of common practice among the Japanese population (11). Duodenal FCL seems to share some common characteristics with nodal ones such as the indolent nature, the female predominance, the occurrence in the fourth or fifth decade of life and a supposed excellent outcome (12). Moreover, a predilection for the second portion of the duodenum in the region surrounding the ampulla of Vater has been noted by some authors. Several hypotheses have been raised in order to explain this characteristic. Firstly, a regional quantitative difference in the amount of intestinal lymphoid tissue and secondly, a possible role of bile salts and pancreatic juice in acting as a carcinogen stimulation (13). Adjunctively, regional lymphnode involvement has frequently been found in duodenal FCLs, even if the primary lesion only involves the submucosal layer. This may be due to the regional anatomical peculiarities with intricate muscular layers allowing lymphoma cells to easily infiltrate regardless of biological intrinsic aggressiveness or systemic diffusion tendency (14). Treatment options have been various such as surgical resection, radiation therapy (RT), chemotherapeutic agents (CT), immunomodulator, eradication therapy and several therapeutic combinations (Table I) but a combined CT-immunotherapy approach could be considered as a standard option (15). Generally

Table 1. — **Overview of all reported cases**

Reference	Pts	Sex	Duodenal	Grade	Stage	Therapy	Outcome Portion
CT-Rituximab							
Ahmed *et al.* (19)	1	F	2nd	1	IIA	CVP ; R	CR at 2 years
Esaki *et al.* (20)	1	M	1st - 2nd	NR	IIA	R-CHOP	PR at 6 months
Aguiar *et al.* (21)	1	NA	NA	NA	I	R	CR
Tsujioka *et al.* (22)	8	4F/4M	Ampulla of Vater	1	IAE	R-CHOP	7/8 CR at 39 months
Isogai *et al.* (23)	1	NA	NA	NA	NA	R-CHOP	NA
Al-Salman *et al.* (24)	1	M	Whole jejunum/3rd	NR	IV	R-CHOP	CR after therapy
CT-Rituximab-RT							
Zenda *et al.* (25)	1	F	Ampulla of Vater	1	I	R-CHOP ; 4Gy RT	CR after therapy
Exclusive surgery							
Tanaka *et al.* (14)	1	F	3rd	1	IA	PD	NR
Matsuzawa (26)	1	F	2nd	3	II1	PD	CR at 2 years
						Adiuvant CT	
Yoshino *et al.* (15)	5	F	2nd	1	I-II	S	Alive at 2-50 months
Surgery + RT							
Misdraji *et al.* (13)	1	F	Ampulla of Vater	1	II	10 Gy Pre-op RT PD 36 Gy Post-op RT	CR after 5 months
Eradication therapy							
Higuchi *et al.* (27)	1	M	2nd/jejunum	1	I	LAC	SD at 5 months
Toyoda *et al.* (28)	1	M	Ampulla of Vater	2	IE	LAC	CR at 2 years
Exclusive radiation							
Takamura *et al.* (29)	1	M	2nd – 3rd	1	IA	30 Gy RT	CR at 3 years
Miscellaneous							
Bende *et al.* (12)	3	3 F	Duodenum	NR	IE	2 RT only 1 CT only	NED at 24-60 months
Born *et al.* (30)	1	F	Whole/jejunum	1	IA	None	NR
Nakase *et al.* (31)	1	F	Papilla of Vater	NR	IA	NR	NR
Mori *et al.* (32)	1	NA	NA	NA	NA	NA	NA
Tang *et al.* (33)	1	M	2nd	NR	I	None	SD
Ridondo-Cerezo (34)	1	F	2nd	NR	NR	Laparoscopy/CT	NR
Katsuki *et al.* (35)	1	NA	NA	NA	Early	S	NA
Takikawa *et al.* (36)	1	NA	NA	NA	NA	S	NA
Sasaki *et al.* (37)	1	NA	NA	NA	NA	R	NA
Sato *et al.* (11)	40	17 F 23 M	38 2nd 2 2nd + 3rd	4 G2 36 G1 3 III E	30 IE 7 IIE	13 O 5 PD 3 ppD 2 CT 2 R-CT 5 E 1 E + R-CT 1 CT-RT 8 NR	13 AWD 2-61 mo 5 NED 17-50 mo 3 NED 13-32 mo 2 AWD at 4-5 mo 1 NED at 24 mo 1 AWD at 12 mo 5 AWD at 6-60 mo 1 NED at 12 mo 1 NED at 18 mo NR
Shia *et al.* (38)	10	7 M 3 F	7 duodenum 3 duodenum/jejunum	6 G1 4 G2	6 IE 4 IIE	3 O 2 S 1 S + CT 3 CT 1 CT/RT	AWD at 2-69 mo 1 NED at 33 mo/1 DOD NED at 73 mo 2 NED at 10-55mo 1 AWD at 6 mo 1 AWD at 44 mo

F : female ; M : male ; NA : not available ; NR : not reported ; R : rituximab ; CVP : cyclophosphamide, vincristine, prednisone ; CHOP : cyclophosphamide, doxorubicin, vincristine, prednisone ; CR : complete remission ; PR : partial remission ; SD : stable disease ; NED : no evidence of disease ; AWD : alive with disease ; LAC : lansoprazole, amoxicillin, clarithromycin ; O : observation ; CT : chemotherapy ; RT : radiotherapy ; S : surgery ; PD : pancreatoduodenectomy ; ppPD : pylorus preserving pancreatoduodenectomy ; E : eradication ; NR : no response.

speaking, FCL is usually characterised by an indolent course and a median survival of 10 years or even more. The vast majority of strategies employed in FL patients with curative intent achieves complete remission in most patients. Unfortunately, the clinical course is usually characterised by multiple relapses. Regardless of the initial treatment chosen, most patients eventually die of lymphoma (16). The use of combination CT guaranteed a major impact in terms of high complete remission rates but did not change the overall survival pattern. High dose therapy with autologous bone marrow transplantation, given either to consolidate remission or as an upfront strategy, may improve remission duration, but it has not shown to improve survival. On the contrary, incumbent toxicity in terms of myelodysplastic syndromes has been described. Most studies suggest that early treatment dose not appear to prolong the survival of asymptomatic patients. In this context, the observation from Stanford of an equal survival between asymptomatic patients managed with expectancy until symptoms appear and those deemed to need therapy immediately properly led to the widespread acceptance of the so called 'benign neglect'(15). More recently, the anti CD-20 monoclonal antibody Rituximab proved to be effective against CD-20 positive low-grade follicular lymphoma, with high response rates in combination with conventional CT and even in CT-refractory patients. Adjunctively, treatment-related toxicity has been reported to be mild and primarly limited to infusion-related events (17). Our group previously reported on the use of rituximab and radiation in localized nodal and extranodal FCL (18), with promising results either in terms of disease control (both local and systemic) and treatment-related toxicity. In this context, in order to combine and effective local treatment with a systemic approach able to clear bone marrow from neoplastic clones, with a concomitant attention towards a low toxicity profile we chose to treat the patient with combined rituximab and radiation. In this way we have been able to perform a conservative approach, avoiding both surgical excision (which might have been associated with a high morbidity considering the anatomical site involved) and CT-related side effects and sequelae with an excellent clinical outcome. The sequential approach (rituximab prior to consolidation radiotherapy) lead to the possibility of a shrinkage of the duodenal lesion allowing the reduction of both radiation treatment volumes and doses, diminishing the probability of RT-related acute and chronic effects.

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