Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-022-07498-5

DDS–SIRC COOPERATIVE CONFERENCES

Duodenal Follicular Lymphoma: Track or Treat?

M. Varanese[1] · A. Lauro[1] · I. Lattina[1] · D. Tripodi[1] · T. Daralioti[2] · S. Khouzam[3] · I. R. Marino[3] · V. Stigliano[2] · V. D'Andrea[1] · S. Frattaroli[1] · S. Sorrenti[1]

Accepted: 4 March 2022

Abstract
Duodenal follicular lymphoma (DFL) is a rare variety of non-Hodgkin's lymphoma of the gastrointestinal tract that usually carries a favorable course, recognized as a new entity in 2016. It is usually diagnosed at an early stage located predominantly in the second portion of the duodenum. We report the case of a 74-year-old male patient with epigastric pain in whom gastroscopy revealed white mucosal nodules that were pathologically diagnosed as grade 1–2 DFL. Staging investigations revealed secondary lesions in the spleen and at the base of the tongue together with latero-cervical adenopathy. The tumor was stage IV according to the Lugano staging system. We reviewed the recent (last five years) literature defining the importance of combination therapy in the advanced stage. The patient achieved complete remission of the disease through chemoimmunotherapy following the Rituximab–Bendamustine scheme.

Keywords Follicular lymphoma · Duodenum · Chemoimmunotherapy · Literature review

Abbreviations

DFL	Duodenal follicular lymphoma
WHO	World Health Organization
EGD	Esophagogastroduodenoscopy
PET-CT	Positron emission tomography-Computed tomography
GI	Gastrointestinal
CVP	Cyclophosphamide, vincristine and prednisone
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone

Introduction

Duodenal-type follicular lymphoma (DFL) is a rare variety of non-Hodgkin's lymphoma of the gastrointestinal tract [1]. DFL was recognized as a new entity by the 2016 World Health Organization (WHO) classification update [2]. While it is predominantly located in the second portion of the duodenum, it may also be present in the stomach, small intestine, colon, and rectum. It is generally an indolent disease with a favorable clinical course [3, 4]. Different approaches have been reported in the literature, including "watch and wait," radiotherapy, therapeutic monoclonal antibodies such as rituximab, and chemotherapy [5, 6]. We present the case of a 74-year-old male patient with primary DFL who had secondary lesions in the spleen and at the base of the tongue together with latero-cervical adenopathy.

Case Report and Evolution

A 74-year-old male patient with a three-month history of epigastric pain was admitted on June 2021 to the esophagogastroduodenoscopy (EGD) service as an outpatient. He had no chronic gastric disease or family history of gastrointestinal neoplastic disorders. Upper endoscopy revealed white mucosal nodules between the second and third duodenal portions (Fig. 1A). Biopsies of these lesions revealed multiple

A profile of Marzia Varanese is available at https://doi.org/10.1007/s10620-022-07499-4.

✉ I. Lattina
ilario.lattina@libero.it

[1] Department of Surgical Sciences, Sapienza University, Rome, Italy

[2] Gastroenterology & Digestive Endoscopy, IRCCS Regina Elena National Cancer Institute, Rome, Italy

[3] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Published online: 08 April 2022

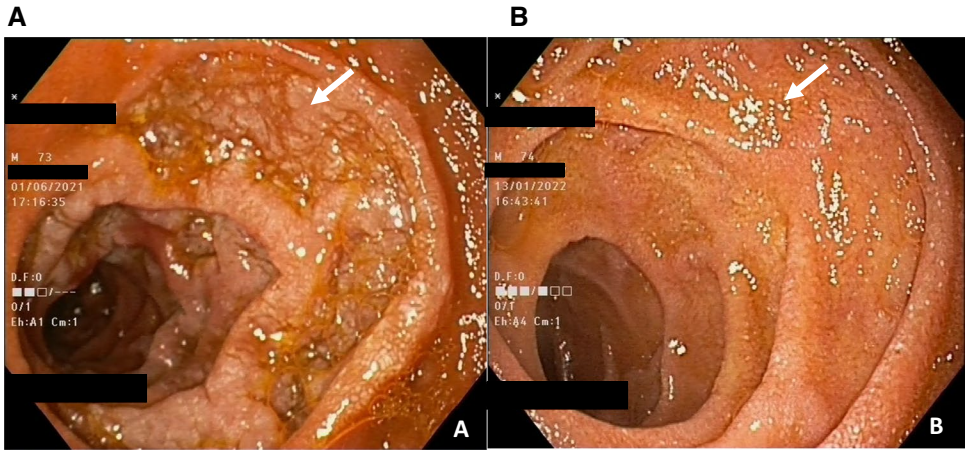

Fig. 1 Endoscopic findings of the second portion of duodenum, **A** white mucosal nodules (white arrow) spread over the duodenum at the diagnosis. **B** the duodenal lesions disappeared after chemoimmunotherapy (white arrow)

lymphoid follicles in the lamina propria. An immune-histochemical study revealed atypical lymphoid cells positive for CD20, CD10, Bcl-6, and Bcl-2, negative for CD5 and cyclin D1 (Fig. 2A, B, and C). The rapid urease test identified no evidence of *Helicobacter pylori*. These data were used to diagnose a DFL of pathological grade 1–2 according to the WHO classification [4]. To complete staging, the patient underwent negative colonoscopy and a total body PET-CT scan, which showed a thickening of the duodenal wall (Fig. 3A), a lesion on the posterior side of the spleen, right latero-cervical adenopathy, and tissue thickening at the base of the tongue. According to the Lugano staging system, the tumor was at stage IV [7]. After oncologic counseling, the patient underwent six cycles of chemo-immunotherapy

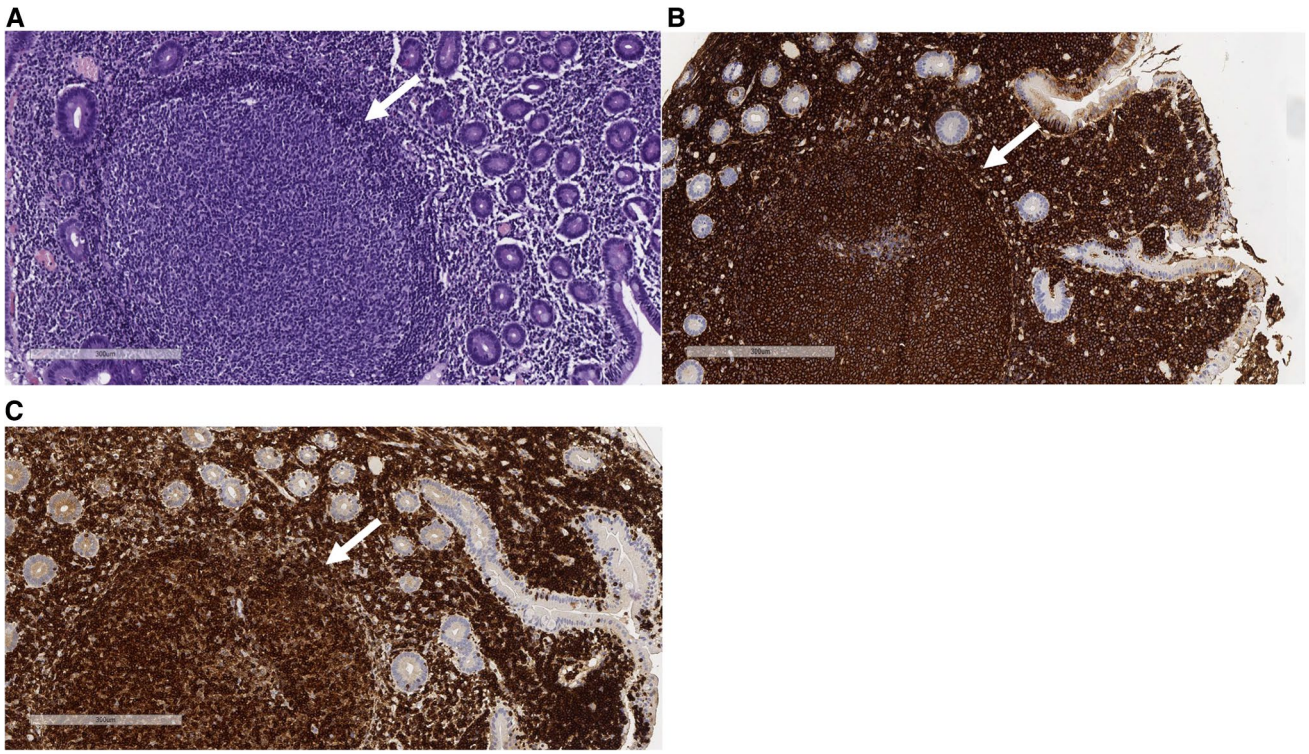

Fig. 2 Histological images. **A** Follicular lymphoma represented by an enlarged follicle without a mantle zone (white arrow). Lymphoma cells are found outside the follicles. Tumor cells are germinal center-derived B-cells and are composed of small to medium-sized cleaved cells (centrocytes) and large noncleaved cells (centroblasts) (hematoxylin–eosin, original magnification × 10). **B** CD20 immunohistochemistry stain reveals that the lymphocytes are predominantly of B-cell lineage (original magnification × 10) (white arrow). **C** Follicular lymphoma stained with Bcl-2 antibody (original magnification × 10) (white arrow)

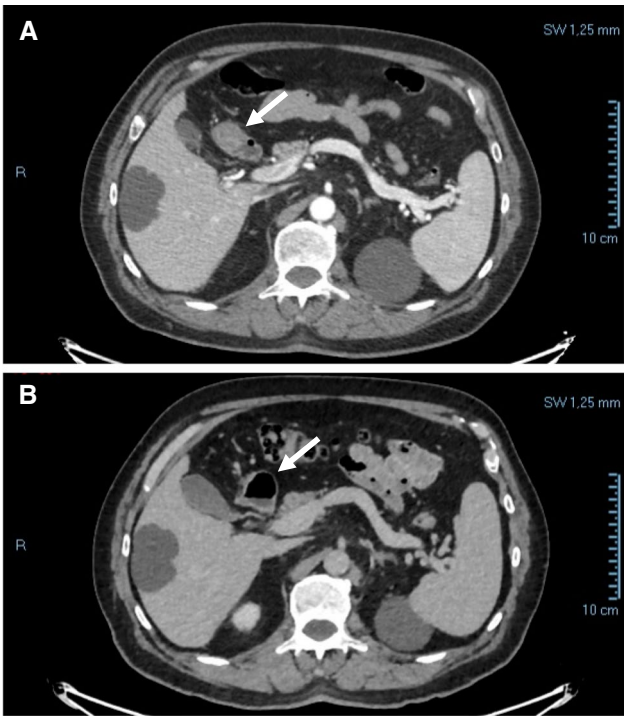

Fig. 3 PET-CT scan of the abdomen. **A** initial image at the diagnosis showing duodenal lesion (white arrow). **B** imaging shows complete resolution of disease after treatment (white arrow)

every 28 days, according to the Rituximab–Bendamustine scheme [8]. After four cycles, he had a second total body PET-CT scan showing complete remission of the disease (Fig. 3B). One month later (January 2022) the patient received a follow-up EGD (Fig. 1B) that revealed complete resolution of the neoplastic lesions.

Discussion

DFL is a subtype of follicular lymphoma considered to be an indolent, slowly progressive tumor with a moderately good prognosis [9]. DFL is usually manifested as a low-grade lesion (grades 1–2). Though it is primarily localized in the second portion of the duodenum, it can develop throughout the whole gastrointestinal tract. Patients with DFL are frequently asymptomatic, rarely reporting GI-related symptoms. DFLs are occasionally diagnosed incidentally in middle-aged patients undergoing endoscopy with the typical mucosal appearance of white nodular or polypoid lesions with a diameter of 1–5 mm [9]. It is important to define the histological classification of the biopsies, which is assessed based on the average number of centroblasts per high-powered field. Grade 1, 2, and 3A lymphomas should be treated as an indolent disease, whereas grade 3B lymphomas are considered aggressive [10]. We performed an international literature review of the therapeutic approach over the last five years, identifying 22 DFL-related publications. The selected articles date from 2017 to 2021 since DFL was not recognized as a new entity until the 2016 WHO classification update [2].

Twelve publications were case reports (Table 1). Five patients at stage I followed the "watch-and-wait" strategy, four of which achieved complete remission [11–14] with one progressing to diffuse large B-cell lymphoma [15]. Three patients received rituximab monotherapy. One patient showed complete regression after one cycle, and the other two patients developed a recurrence, and both underwent an additional cycle of rituximab [16–18]. Complete regression of the intestinal lesions was also noted in one patient receiving clarithromycin monotherapy [19]. Two cases performed an invasive treatment (papillectomy and pancreaticoduodenectomy) with a complete resolution [20, 21]. Lastly, one case did not report therapeutic management [22].

Moreover, we reviewed four retrospective papers reporting a DFL clinical series (Table 2) [23–26]. According to the literature, there are several therapeutic approaches, including "watch and wait," radiotherapy, rituximab-chemotherapy with cyclophosphamide, vincristine, doxorubicin, prednisone (R-CHOP), and rituximab alone [27]. In patients at stage I–II, the first-line treatment is represented by radiotherapy. As alternatives to radiotherapy, the "watch-and-wait" approach or rituximab monotherapy may also be considered but only in selected cases [9, 25]. The "watch-and-wait" strategy has been considered a valid option in many studies, generally applied to asymptomatic patients without systemic involvement [28–31].

Optimal therapy has not yet been clearly established in patients with advanced-stage III-IV (such as our patient). In 10–20% of cases, the disease shows spontaneous regression. Therapy should be considered when patients have symptoms, organ dysfunction, cytopenias secondary to lymphoma, bulky disease, or a rapid progression. According to the guidelines of the National Comprehensive Cancer Network 2021 [8], patients with an advanced stage should receive as first-line therapy (1) rituximab or obinutuzumab in combination with bendamustine, (2) CHOP and rituximab or obinutuzumab, (3) CVP and rituximab or obinutuzumab, (4) lenalidomide and rituximab [8].

Only one publication in the literature reported on a DFL patient at stage IV, as in our case [21]. The patient had obstructive jaundice with a CT scan revealing a lesion involving the second duodenal portion, the head of the pancreas, and the common bile duct. Malignancy was never histologically proved pre-operatively. Since pancreatic adenocarcinoma was suspected, the patient underwent pancreaticoduodenectomy, with the diagnosis of DFL confirmed on the surgical specimen.

Table 1 Case reports of DFL

Reference	Author	Year	Age (years)	Sex	Clinical Features	Histologic grade of DFL	Lugano stage at diagnosis	Management	Lesions other than duodenum	Follow-up
11	Garrido	2021	79	M	No symptoms	1	I	Watch and wait	None	CR
12	Silva	2021	83	F	No symptoms	1	I	Watch and wait	None	CR
16	Gioitis	2021	54	F	No symptoms	3	NA	Rituximab	Rectum and stomach	CR
13	Wu	2021	48	F	Obstructive jaundice	1	I	Watch and wait	None	CR
14	Charoenlap	2021	74	M	Epigastric pain	1	I	Watch and wait	None	CR
20	Takashi	2020	70	F	No symptoms	1	II 1	Papillectomy plus watch and wait	Lymph node	CR
17	Cencini	2020	67	M	Abdominal pain	1	I	Rituximab	None	RituximabrecurrenceBendamustine + Rituximab followed by CR
22	Nann	2019	84	M	NA	NA	NA	NA	NA	NA
15	Tanigawa	2019	52	M	Abdominal pain	1	I	Watch and wait	Ileum	Progression to diffuse large B-cell lymphoma
21	Sato	2019	72	M	Obstructive jaundice	3a	IV	Pancreaticoduodenectomy	Pancreas and common bile duct	CR
19	Kiesewetter	2018	58	M	Abdominal pain	1	I	Clarithromycin	None	CR
18	Nehme	2017	51	F	Dyspepsia	1	I	Rituximab	None	CR62months recurrenceRituximab followed by CR

NA not available; *CR* complete remission

Table 2 Clinical series of DFL

Ref	Author	Year	N. pts	Median age	M/F	Clinical features	Histologic grade of DFL 1–2-3	Lugano stage at diagnosis I-II-III-IV	Rituximab	Watch and wait	Chem-other-apy	Surgery	Radiotherapy	R-CHOP	Remission	Progression
23	Saburi	2020	23	65	13/10	No symptoms	15–3-NA	11–7-0–1	3	14	0	2	0	4	21	2
24	Abe	2020	18	66.5	13/5	15 no symptoms—3 symptoms	15–3-0	18–0-0–0	5	10	0	0	1	2	NA	5
25	Lee	2019	20	NA	6/14	17 no symptoms -3 symptoms	19–0-1	18–1-0–1	0	0	1	0	19	0	20	0
26	Inoue	2020	30	59.5	10/20	21 no symptoms -9 symptoms	NA	24–4-0–1	2	22	0	0	2	4	28 R- 2 NA	NA

NA not available; *R* remission; *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; *N. pts* number of patients

On the contrary, our patient received an early endoscopic diagnosis of DFL and underwent chemo-immunotherapy according to the Rituximab–Bendamustine scheme for six cycles, with complete remission of the disease.

Conclusions

DFL was recognized as a new entity in 2016, and there is still debate on its therapeutic approach, especially at advanced stages. In our case, we used a Rituximab–Bendamustine scheme with success, but further clinical studies are necessary in order to establish the most appropriate therapies.

Key Messages

- DFL is a new entity, originally identified in 2016
- The clinical course is usually favorable
- There is debate regarding the therapeutic approach at advanced stages

Declarations

Conflict of interest The authors have no conflicts of interest to declare regarding this case presentation.

References

1. Hellmuth JC, Louissaint A, Szczepanowski M et al. Duodenal-type and nodal follicular lymphomas differ by their immune microenvironment rather than their mutation profiles. *Hematology Am Soc* 2018;132:16.
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.
3. Takata K, Okada H, Ohmiya N et al. Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity a multicenter, retrospective analysis in Japan. *Cancer Sci* 2011;102:1532–1536.
4. Campo E, Swerdlow SH, Harris NL et al. The 2008 WHO classification of lymphoid neoplasms and beyond evolving concepts and practical applications. *Blood* 2011;117:19.
5. Tari A, Kitadai Y, Mouri R et al. Watch-and-wait policy versus rituximab-combined chemotherapy in Japanese patients with intestinal follicular lymphoma. *J Gastroenterol Hepatol* 2018;33:1461–1468.
6. Harada A, Oguchi M, Terui Y et al. Radiation therapy for localized duodenal low-grade follicular lymphoma. *J Radiat Res* 2016;57:412–417.
7. Cheson BD, Fisher RI, Barrington SF et al. Reccommendations for initial evaluation, staging and response assessment of Hodgkin

and Non-Hodgkin lymphoma the Lugano classification. *J Clin Oncol* 2014;32:27.
8. NCCN Clinical Practice Guidelines in Oncology 2021. B-Cell Lymphomas. https://www.nccn.org/guidelines/guidelines-with-evidence-blocks.
9. Marks E, Shi Y. Duodenal-type follicular lymphoma. A clinicpathological review. *Arch Pathol Lab Med* 2018; 142:542–547.
10. Dreyling M, Ghielmini M, Rule S et al. Newly diagnosed and relapsed follicular lymphoma ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021;32:298–308.
11. Garrido I, Santos-Antunes J, Cardoso H, et al. Duodenal-type follicular lymphoma-a silent tumor. *Rev Esp Enferm Dig* 2021 Sep 14 (online ahead of print).
12. Silva JF, Morais R, Fonseca E, et al. A case of duodenal-type follicular lymphoma. *Rev Esp Enferm Dig* 2021 Sep 2 (online ahead of print).
13. Wu YL, Tsai YN, Wang WL. Magnifying observation of duodenal follicular lymphoma with chromoendoscopy and narrow-band imaging. *Gastrointest Endosc* 2021;94:1150–1151.
14. Charoenlap C, Akarapatima K, Suwanno K et al. Primary follicular lymphoma of the duodenum a case report and review of literatures. *Gastroenterol Hepatol Bed Bench* 2021;14:185–189.
15. Tanigawa T, Abe R, Kato J et al. Histological transformation in duodenal-type follicular lymphoma a case report and review of the literature. *Oncotarget* 2019;10:3424–3429.
16. Giotis I, Tribonias G, Zacharopoulou E et al. A rare case of duodenal-type follicular lymphoma in rectum appearing as hyperplastic polyp with metachronous appearance in duodenum and stomach. *Clin J Gastroenterol* 2021;14:1632–1636.
17. Cencini E, Fabbri A, Mecacci B et al. Is bendamustine plus rituximab a suitable option for rituximab-refractory duodenal-type follicular lymphoma? *Acta Gastroenterol Belg* 2020;83:493.
18. Nehme F, Rowe K, Palko W et al. Primary duodenal follicular lymphoma with late disseminated nodal relapse responsive to rituximab monotherapy A case report. *Mol Clin Oncol* 2017;7:911–914.
19. Kiesewetter B, Dolak W, Mayerhoefer ME et al. Successful Clarithromycin Monotherapy in a Patient with Primary Follicular Lymphoma of the Duodenum. *Case Rep Oncol* 2018;11:239–245.
20. Takashi A, Kosuke K, Takayuki N et al. Follicular lymphoma Grade 1 of the minor duodenal papilla successfully diagnosed by endoscopic papillectomy. *Endoscopy* 2021;53:35–37.
21. Sato J, Ishiwatari H, Ashida R et al. Primary non-ampullary duodenal follicular lymphoma presenting with obstructive jaundice. *Clin J Gastroenterol* 2020;13:214–218.
22. Nann D, Bonzheim I, Müller I et al. Clonally related duodenal-type follicular lymphoma and in situ follicular neoplasia. *Haematologica* 2019;104:537–539.
23. Saburi M, Kondo Y, Ogata M et al. Development of diffuse large B-cell lymphoma from duodenal type follicular lymphoma a retrospective study of 23 cases. *Int J Hematol* 2020;112:658–665.
24. Abe R, Mori T, Tanigawa T et al. Clinical characteristics and outcomes of duodenaltype follicular lymphoma. *Leuk Lymphoma* 2020;61:3266–3268.
25. Lee H, Oh D, Yang K et al. Radiation Therapy Outcome and Clinical Features of Duodenal-Type Follicular Lymphoma. *Cancer Res Treat.* 2019;5:547–555.
26. Inoue H, Rai S, Tanaka H et al. Tumour-immune microenvironment in duodenal-type follicular lymphoma. *Br J Haematol* 2020;191:243–252.
27. Duffles Amarante G, Collins G, Rocha V. What do we know about duodenal-type follicular lymphoma? From pathological definition to treatment options. *Br J Haematol* 2020;188:831–837.
28. Schmatz AI, Streubel B, Kretschmer-Chott E et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma a retrospective study of 63 cases. *J Clin Oncol* 2011;29:1445–1451.
29. Misdraji J, Harris NL, Hasserjian RP et al. Primary follicular lymphoma of the gastrointestinal tract. *Am J Surg Pathol* 2011;35:1255–1263.
30. Mori M, Kobayashi Y, Maeshima AM et al. The indolent course and high incidence of t(14;18) in primary duodenal follicular lymphoma. *Ann Oncol* 2010;21:1500–1505.
31. Yanai S, Nakamura S, Takeshita M et al. Translocation t(14;18)/IGH-BCL2 in gastrointestinal follicular lymphoma correlation with clinicopathologic features in 48 patients. *Cancer* 2011;117:2467–2477.