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Non–Hodgkin's Lymphoma of the Appendix

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Abstract

Infiltration of the appendix as a manifestation of non-hodgkins lymphoma (NHL) at diagnosis or at relapse is a rare finding. We report the history of a patient with gastrointestinal non-hodgkin's lymphoma treated 8 years earlier who presented with symptoms suggestive of acute appendicitis secondary to relapsed NHL.

Keywords: Non Hodgkins Lymphoma, Diffuse Large B Cell Lymphoma, appendix, PET CT

1. Introduction

Non-hodgkin's lymphomas (NHL) typically arise in the lymph nodes, spleen, Waldeyer's ring and thymus. However approximately one third are extra-nodal (Zucca et al., 1997, 1999). The gastrointestinal tract is the predominant site of extranodal NHLs, and incidence at this site is increasing (Crump, Gospodarowicz, & Shepherd, 1999). However, infiltration of the appendix as a manifestation of NHL is a rare finding and reports of a relapsed lymphoma of the appendix are even more uncommon.

2. Case Report

A 61 year old woman was initially diagnosed with gastrointestinal NHL in 2006 after presenting with epigastric pain, dyspepsia and weight loss. She denied any history of coeliac disease. A gastroscopy demonstrated a 4.25cm large ulcer at the angulus of the stomach. Biopsy confirmed a diagnosis of diffuse large B-cell NHL of the stomach. Staging scans and bone marrow aspirate did not reveal any evidence of metastatic disease. She completed six months of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) to complete remission (CR).

Eight years on from her original diagnosis she attended our surveillance outpatient clinic and reported a six month history of dull right iliac fossa pain and flu-like symptoms. She denied any weight loss or night sweats. Physical examination revealed a soft abdomen with tenderness on deep palpation of the right iliac fossa. No mass was palpable and there was no rebound tenderness. There was no evidence of lymphadenopathy. A routine blood panel was unremarkable except for raised LDH (lactate dehydrogenase) levels at 236 units/l (120-220 IU/l) and beta2 microglobulins were elevated at 5.7mg/l (1.2-2.4 mg/l). Anti-TTG (anti-transglutaminase) antibodies were negative at 2.7 u/ml.

A staging CT PET demonstrated increased fluorodeoxyglucose (FDG) uptake at the appendix (SUV max 31) (Figure 1) and mild uptake at the fundus of the stomach. Gastroscopy and biopsies were normal. Colonoscopy showed abnormal swelling of the ileocecal valve however biopsies from this area were also indeterminate. After discussion at a multi-disciplinary meeting (MDM) a decision was made to proceed to an appendectomy.

At surgery it was demonstrated that the appendix had perforated and there was an appendiceal mass adhering to the anterior abdominal wall. Laparoscopy was converted to an open resection with appendectomy and ileocolic resection with side-to-side ileocolic anastomosis.

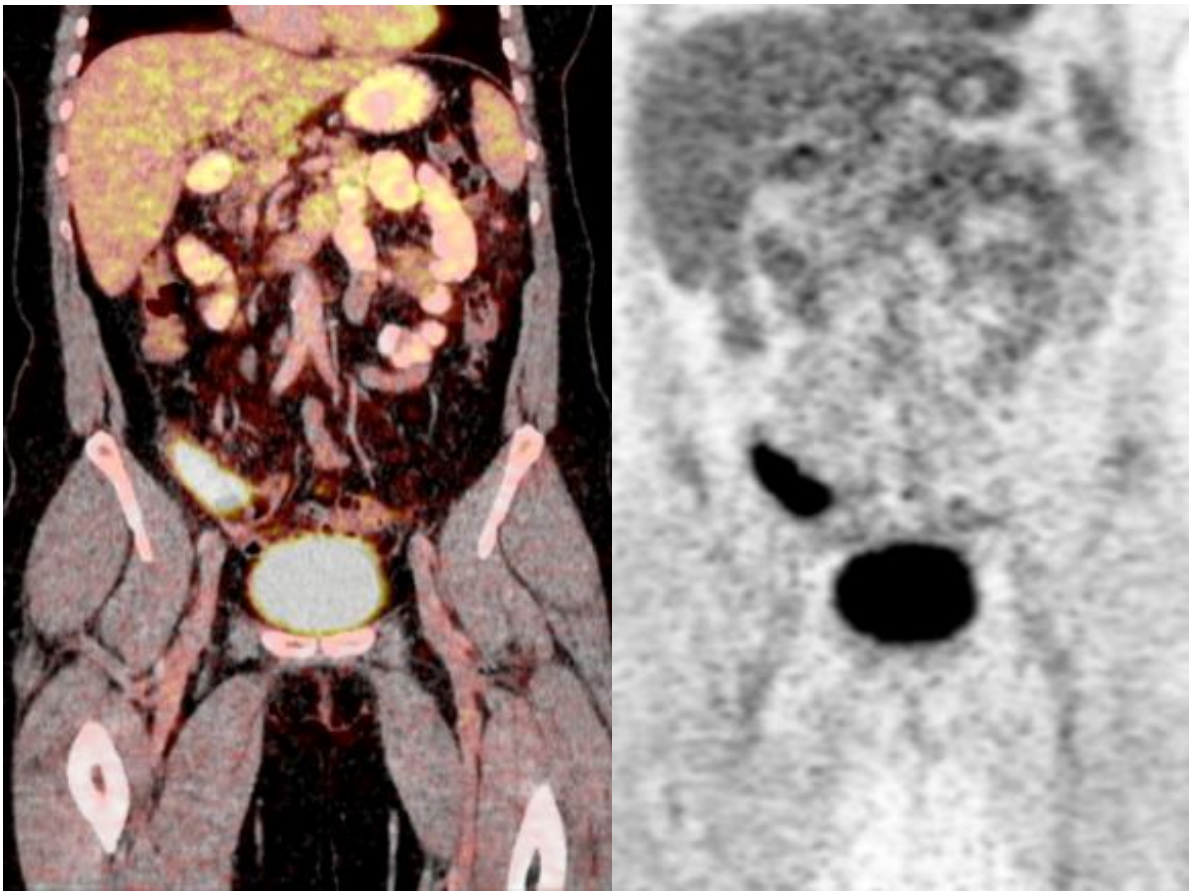

Figure 1. Coronal images from PET CT. Markedly abnormal FDG activity (SUV max 31) within the appendix and caecum

Histology from the surgical specimen demonstrated an atypical lymphoid infiltrate of intermediate to large cells involving the full thickness of the appendiceal wall (Figure 2). Immunohistochemistry was positive for CD45, CD20 and BCL6 and negative for MUM-1, CD10, BCL2 and Cyclin D1. MIB1 proliferation index was 85%. These findings were felt to be consistent with relapsed diffuse large B cell, germinal centre subtype, NHL. Subsequent bone marrow biopsy showed one intratrabecular lymphoid aggregate with increased reticulin suspicious for involvement.

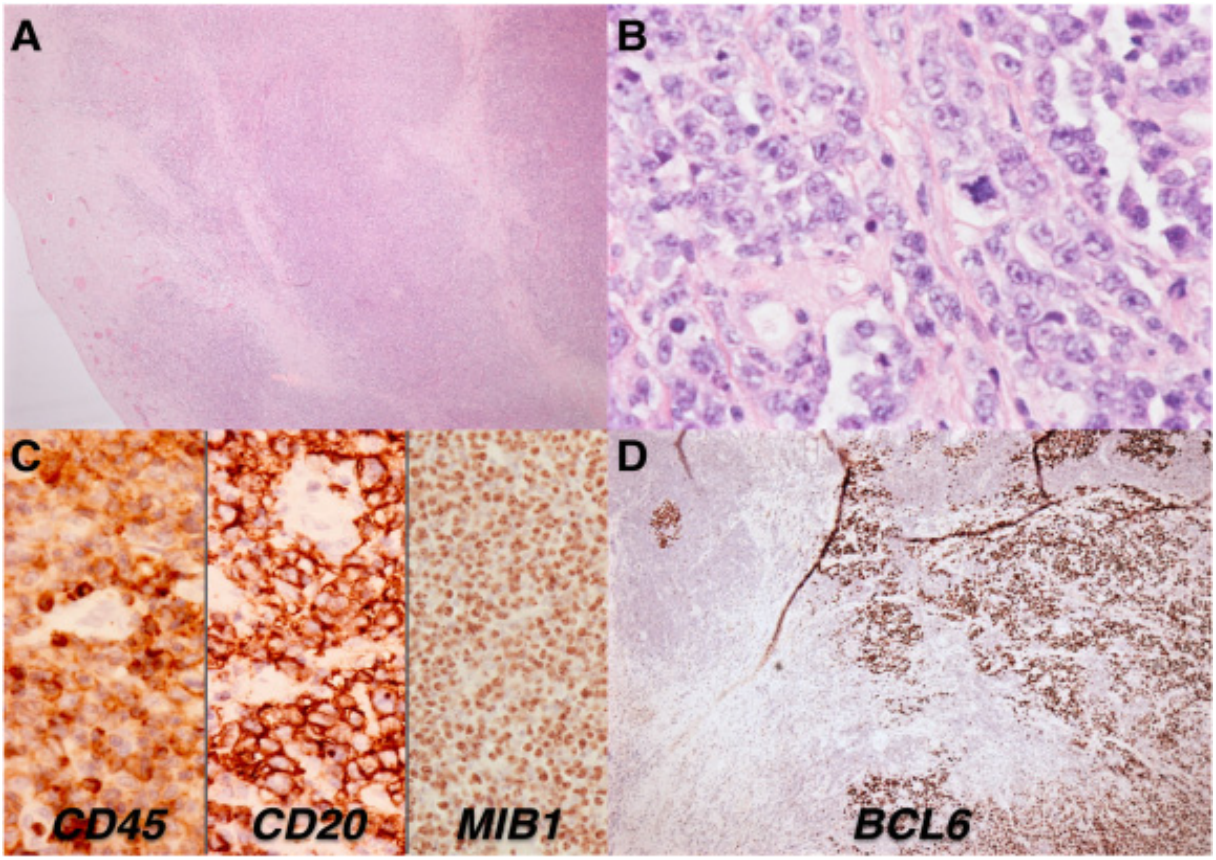

Figure 2. Diffuse Large B Cell of the Appendix. The appendix wall showed a transmural infiltrate (A) of intermediate to large atypical cells (B). The neoplastic cells were positive for CD45 and CD20, while CD3 and CD5 highlighted a background population of T cells, confirming a Diffuse Large B Cell lymphoma (C). The neoplastic cells stained with BCL6, consistent with germinal centre B-cell like cells (D). MIB1 demonstrated a proliferation index of 85% (C)

After review at a multidisciplinary meeting she was treated with salvage RICE (Rituximab, Ifosfamide, Carboplatin, Etoposide) chemotherapy followed by autologous bone marrow transplant. Her end of treatment day 100 CT PET showed a complete remission (CR) (Figure 3). At her most recent follow up 9 months after CR, there was no evidence of recurrence.

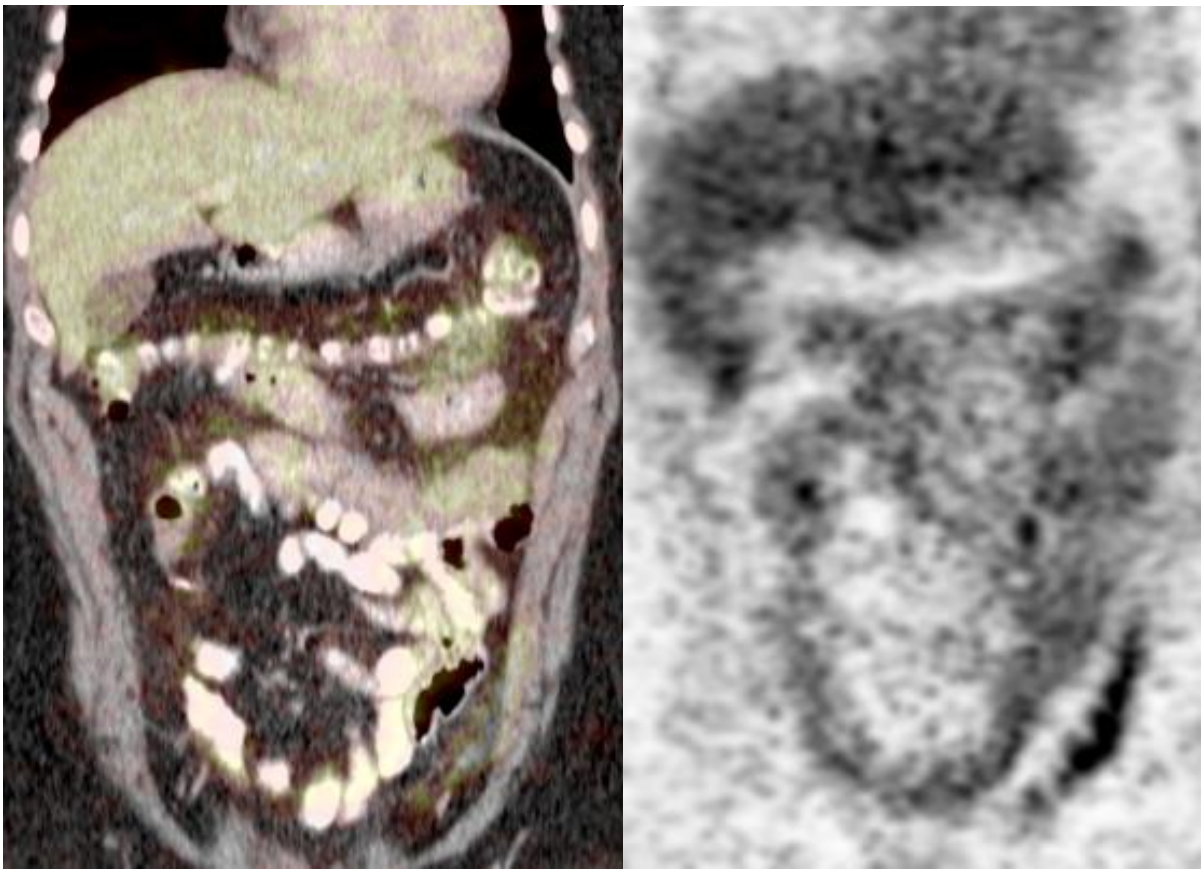

Figure 3. PET CT coronal image. No evidence of abnormal FDG activity

3. Discussion

The gastrointestinal tract is well established as the most common site of extranodal lymphoma by NHLs. Involvement of the appendix is an exceedingly rare finding and has been described only in isolated case reports (Table 1). To our knowledge, only four cases of recurrent lymphoma in the appendix have been reported in the literature (Tsujimura et al., 2000; Katz, Stein, & Mazzie, 2002; Pickhardt et al., 2002; Chae, Kumar, & Cheema, 2015).

Table 1. Literature review of primary lymphomas of the appendix. Right lower quadrant (RLQ), Right iliac fossa (RIF), Diffuse Large B cell Lymphoma(DLBCL), Natural Killer (NK), Gastrointestinal (GI), Acquired Immunodeficiency Sundrome (AIDS)

References	**Year**	**Number of Cases studied**	**Number of Appendiceal Lymphomas**	**Primary or Relapse (Time to relapse)**	**Age (yrs)**	**Presenting Symptoms**	**Primary Lymphoma type (site)**
Present Case	2015	1	1	Relapse (8 years)	61	RLQ pain	DLBCL
Tsujimara et al. (4)	2000	1	**1**	Relapse (8 months)	20	RLQ pain	NK/T-cell Lymphoma (Nasal)
Katz et al. (5)	2002	1	**1**	Relapse (9 years)	66	Rectal bleeding	Large cell, B cell type

Pickhardt et al. (6)	2001	5	**5**	Relapse x 1* (6 years)	Mean 54 years	RLQ pain/fever x 3 Lower GI bleeding x 1, Fever/rigors x 1	Mantle cell lymphoma x 2 DLBCL x 1 *Non-Hodgkin's Lymphoma consistent with DLBCL x 1 Large cell undifferentiated malignancy consistent with DLBCL x 1
Chae et al. (7)	2015	1	**1**	Relapse (3 years)	75	RLQ pain	Mantle Cell Lymphoma
Kitamura et al. (8)	2000	1	**1**	Primary	84	RLQ pain	T-Cell Non-Hodgkin's Lymphoma
Muller et al . (9)	1997	4	**3**	Primary	24,69,74	RLQ pain	Diffuse Large, B-Cell (Undifferentiated) Anaplastic Large T cell Marginal Zone B cell
Rao and Aydinalp (10)	1991	1	**1**	Primary	75	RLQ pain/mass, lower GI bleeding	Lymphoblastic Lymphoma
Fu et al. (11)	2004	1	**1**	Primary	42	RLQ pain, N+V, fever	DLBCL
Carpenter (12)	1991	1	**1**	Primary	65	PR Bleeding	Diffuse malignant lymphoma, small Cell, cleaved type
Pasquale et al. (13)	1994	47 (Literature Review)	**47**	Primary	Mean 25.7 years	RLQ pain x 31, Incidental finding x 5, Non specific symptoms (Abdominal pain, fever, nausea, vomiting, anorexia)	Lymphoblastic sarcoma x 25, Giant Follicular Lymphoblastoma x 9, Lymphosarcoma (unclassified) x 3, Well differentiated lymphocytic x 3, Diffuse large cell x 3, Burkitt's x 3, Unknown x 1
Nanji and Anderson (14)	1983	1	**1**	Primary	22	Epigastric/periunbilical pain	Burkitt's Lymphoma
Caine et al. (15)	1990	1	**1**	Primary	3	RLQ pain	Burkitt's Lymphoma
Shimada et al. (16)	1990	1	**1**	Primary	48	RLQ pain	Diffuse Large B cell
Carstensen and Hoffmann (17)	1993	1	**1**	Primary	17	RLQ pain, fever	Burkitt's Lymphoma
Krepel et al. (18)	1996	1	**1**	Primary	25	RLQ pain	Burkitt's Lymphoma
Bissen et al. (19)	2002	1	**1**	Primary	12	RLQ pain	Burkitt's Lymphoma
Khanna and Buddhavarapu (20)	2008	1	**1**	Primary	49	Upper abdominal pain, nausea/vomiting	Burkitt's Lymphoma
Weine et al. (21)	2009	1	**1**	Primary	76	RLQ pain	Nodular lymphocyte predominant HL
Ghosal and	2014	1	**1**	Primary	2 yrs 10	Weight loss, pallor, diffuse	Hodgkins Lymphoma

Acharyya (22)					months	abdominal pain	
Goncalves et al. (23)	2012	1	**1**	Primary	14	Periumbilical pain, fever, anorexia	Burkitt's Lymphoma
Guo et al. (24)	2014	1	**1**	Primary	43	Lower abdominal pain, nausea/vomiting	DLBCL
Min Baek et al. (25)	2011	1	**1**	Primary	37	RIF pain	DLBCL
Ghasemi and Kenari (26)	2010	1	**1**	Primary	22	RIF pain	DLBCL
Radha et al. (27)	2008	1	**1**	Primary	61	RIF pain, fever	Marginal Zone BCL
Weledji et al. (28)	2014	2	**2**	Primary	13,18	RIF pain x 2	Burkitt's Lymphoma x 2
Bhardwaj et al. (29)	2010	1	**1**	Primary	14	RIF pain, vomiting, diarrhoea	Burkitt's Lymphoma
Tadele and Yancovitz (30)	2007	2	**2**	Primary	66 44	Fever, RIF pain Lower abdominal pain, fever, nausea/vomiting	DLBCL
Shiwani (31)	2006	1	**1**	Primary	-	RIF pain	Malignant lymphoma (Unclassified)
Ziari et al. (32)	2014	3	**3**	Primary	10,23,24	RLQ pain x 3	Burkitts Lymphoma x 3
Abdalla and El-Hennawy (33)	2010	1	**1**	Primary	49	RIF pain, haematuria	Burkitt's Lymphoma
Sharma et al. (34)	2015	1	**1**	Primary	50	Lower abdominal pain	DLBCL
Gaopande et al. (35)	2015	1	**1**	Primary	50	RLQ pain	Mantle cell lymphoma
Matsushita and Takeshita (36)	2013	1	**1**	Primary	7	Acute abdominal pain	T cell NHL

The gastrointestinal tract is the most common site of extranodal lymphoma, these account for 4-20% of all primary NHLs and 30-45% of extranodal cases (d'Amore et al., 1994). Table 2 shows the most common sites of GI extra nodal involvement as reported by the two largest studies of GI lymphoma in Greek (128 patients) and German populations (371 patients) (Koch et al., 2001) (Papaxoinos et al., 2006). The appendix, as a site of lymphoma, is so uncommon that it is often omitted in review articles on NHL of the GI tract (Pickhardt et al., 2002; Levine et al., 1997). To our knowledge there has been only one case series on the topic to date and included only five cases (Pickhardt et al., 2002). Rao and Aydinalp (1991) estimated the incidence of primary appendiceal lymphoma at 0.015% of all appendectomy specimens and in one series of 8699 appendectomy specimens by Carpenter (1991), there were 101 neoplasms of which only three were lymphomas. More recently Fu, Wang and Tseng (1994) described in a review of 4458 appendectomy specimens over a 13 year period, only one case was an appendiceal lymphoma.

Table 2. Common sites of involvement (Koch et al., 2001; Papaxoinos et al., 2006)

Stomach	68-75%
Small bowel (including duodenum)	9%
Ileo-cecal region	7%
More than one GI site	6-13%
Rectum	2%
Diffuse colonic involvement	1%

Primary appendiceal lymphomas are extremely rare, and relapses in the appendix are even more uncommon. The majority of both primary and relapsed appendiceal lymphomas are non-hodgkin's B-cell lymphomas (Carpenter, 1991). Median age at diagnosis for GI tract NHLs is 55 years (Pickhardt et al., 2002), however appendiceal NHLs do manifest earlier in the second or third decade of life (Carpenter, 1991). The most common presenting symptom is abdominal pain, often localized to the right iliac fossa, and associated nausea and vomiting, mimicking acute appendicitis (Table 1). Rarely they may present with lower GI haemorrhage. Pasquale et al. (1994) identified 46 cases of reported appendiceal lymphoma since 1898, and 31 of these patients presented with acute or subacute right lower quadrant pain, while five were incidentally discovered at appendectomy. Patients with appendiceal lymphoma may also complain of anorexia, weight loss, and a right lower quadrant mass may be present at physical examination (Rao & Aydinalp, 1991). Massive enlargement of the appendix may be present and rarely, may lead to intussusception (Rao & Aydinalp, 1991; Carpenter, 1991). In the majority of cases however, clinical findings are often non-specific, thus delaying diagnoses.

As such, the majority of diagnoses are made after surgery, where post-operative histology of the specimen reveals the true diagnosis. Preoperative diagnoses are rare (Pickhardt et al., 2002). On pathological review, diffuse enlargement of the appendix secondary to lymphomatous infiltration is frequently noted, with the average appendiceal diameter measured at 3cm (Pickhardt et al., 2002). That said, the pathogenesis of appendiceal lymphoma remains uncertain, with both intravascular tumour invasion leading to ischaemia of the appendix and subsequent appendicitis or obstruction of the appendiceal lumen leading to appendicitis postulated as mechanisms of promoting dysplasia (Chae, Kumar, & Cheema, 2015).

Reaching the diagnosis radiologically prior to surgery is challenging, and only scant descriptions exist of appendiceal lymphoma revealed on CT (Katz, Stein, & Mazzie, 2002). The five case reports presented by Pickhardt et al. were all retrospectively discovered on CT, three having periappendiceal inflammatory changes (Pickhardt et al., 2002).

Imaging typically shows diffuse enlargement of the appendix in both appendicitis and appendiceal neoplasm, however this may also be misinterpreted as a thickened small bowel loop or an extraintestinal process. A diameter of 6-7mm is well established as the diagnostic threshold for appendicitis on CT and ultrasound, however there is limited data describing the upper limit diameter where infiltrative neoplasms could be considered in the differential (Pickhardt et al., 2002). Inflamed appendices in excess of 15mm are rare (Birnbaum & Wilson, 2000), and imaging from the study by Pickhardt et al., showed diameters greater than 2.5cm (Pickhardt et al., 2002). In that study three of the five patients had associated retroperitoneal or mesenteric adenopathy and of the four patients in whom preoperative CT reports were available, none considered an appendiceal neoplasm prospectively (Pickhardt et al., 2002).

Management of relapsed appendiceal lymphomas is challenging, and there are no clear guidelines due to its rarity. It has previously been postulated that these lymphomas can be successfully treated with an appendectomy, with or without a limited right hemicolectomy (Rao & Aydinalp, 1991). Adjunctive therapy depends on the stage of the disease and the histopathology. Our patient was treated with salvage RICE chemotherapy followed by autologous bone marrow transplant due to her suspicious bone marrow biopsy.

In summary, clinical awareness and suspicion is crucial in achieving the correct diagnosis and initiating treatment. Even without radiological support, physicians should have relapsed lymphoma in their differential when confronted with a patient presenting with GI symptoms, particularly with signs suggestive of appendicitis in those with a background history of lymphoma.

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