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A rare case of primary gastric Burkitt's lymphoma associated with malignant pleural mesothelioma

BACKGROUND: *Primary gastric Burkitt lymphoma (PG BL) and malignant pleural mesothelioma (MPM) are rare and aggressive tumors with poor prognosis. HIV and EBV infection have a link in the aetiology of PG BL, while MPM is usually associated with asbestos exposure.*
Endoluminal bleeding from massive solid tumor, and dyspnea usually due to pleural effusion, are the typical clinical manifestations respectively of PG BL and MPM. In most patients just palliative treatment is indicated.
CASE REPORT: *A caucasian elderly male, negative for the proven risk factors, presenting respiratory failure due to massive left pleural effusion with severe mediastinal shift. Contrast enhanced - Computed Tomography (CE-CT) showed a large mass causing circumferential thickening of the gastric fundus, infiltrating the left diaphragmatic dome and the ipsilateral crus. Macroscopically, on endoscopy the gastric fundus appeared completely occupied by an ulcerated large mass protunding in the gastric lumen. Histopathological examination from biopsy specimens taken during esophagogastroduodenoscopy and thoracoscopy allowed to make diagnosis of PG BL and MPM. The patient first underwent a placement of a chest tube drainage for the pleural effusion and then a thoracoscopic talc insufflation (TTI) in the left hemithorax. A surgical treatment of the gastric lesion was planned, due to the rapid growth and the high risk of bleeding. The patient died because of fatal cardiac arrhythmia, before undergoig abdominal surgery.*
CONCLUSIONS: *This report presents an unique case of PG BL associated with MPM and highlights the real challenge for the physicians to identify them in early stage, especially in patients without the proved risk factors. The onset symptoms make it a very singular case, characterized by severe dyspnea up to respiratory failure, due to massive left pleural effusion and contralateral mediastinal fluttering, without an active bleeding from the gastric mass, while CE-CT findings were instead negative for pleural thickening and positive for circumferential thickening of the gastric fundus.*

KEY WORDS: Burkitt Lymphoma, Case Report, Gastric, Pleural Mesothelioma, Pleural Effusion, Respiratory Failure

Introduction

Primary gastric Burkitt lymphoma (PG BL) is an uncommon type of B-cell lymphoma which is endemic in Africa and may present as a sporadic form in the rest of the world. Sporadic lymphomas most commonly involve the gastrointestinal tract, particularly the ileocecal region, nevertheless PG BL is extremely unusual and only 53 cases have been reported until 2017 worldwide [1]. This neoplasia is a rare finding in adult population testing negative for HIV [2]. The role of both HIV and EBV infection in the aetiology of BL have been confirmed in the past years, while the link between PG BL and Helicobacter pylori (H. pylori) infection is still controversial, and their association is not well defined [3]. In

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ABBREVIATIONS

CE-CT: Contrast enhanced - Computed Tomography
EBV: Epstein-Barr virus
EGDS: esophagogastroduodenoscopy
HE: histopathological examination
HIV: Human Immunodeficiency Virus
H. pylori: Helicobacter pylori
MPM: malignant pleural mesothelioma
NHL: Non-Hodgkin's lymphoma
PG BL: Primary gastric Burkitt lymphoma
TTI: thoracoscopic talc insufflation

case of PG BL both esophagogastroduodenoscopy (EGDS) and contrast enhanced - computed tomography (CE-CT) scan show a massive solide tumor causing endoluminal bleeding [3]. The onset symptoms for PG BL are usually vomiting, acute or chronic bleeding and pain after eating [3]. The standard treatment of BL in gastrointestinal tract is represented by cytoreductive surgery along with chemotherapy [4].
The malignant pleural mesothelioma (MPM) is a rare and very aggressive tumor characterized by poor prognosis. Usually the patient occupational history is important for the diagnostic suspicion, as it is associated with asbestos exposure in >80% of cases [5]. Dyspnea is the typical clinical manifestation, usually due to pleural effusion [6]. A lack of pleural thickening or visible tumor are defined as radiological early MPM [7]. Definitive diagnosis is made by immunohistochemical examination on multiple biopsies taken during thoracoscopy. In most patients just palliative treatment is indicated [8,9].
Clinical association between malignant pleural mesothelioma and primary gastric Burkitt lymphoma has never been found in the literature, so this is the first and unique case of PG BL associated with MPM in caucasian elderly male.

Case Report

We report a case of PG BL associated with MPM in a 80-years-old caucasian male with past medical history of benign prostatic hyperplasia and laryngeal cancer, who was admitted to hospital for respiratory failure.
The patient had no clinical history of occupational exposure to asbestos, and was negative for both HIV infection and EBV infection. H. pylori infection was not investigated prior the time of histopathological diagnosis. The laboratory work-up revealed mild anemia (Hb 11.5 g/dl, normal value (nv) 12.0-16.0 g/dl) and hypoproteinemia (total protein 4.3 g/dl, nv 6.0-8.2 g/dl; albumin 2.9 g/dl, nv 4.02-4.76 g/dl). Tumor markers showed mild positivity for Carbohydrate antigen 19-9 (CA19.9 52 U/ml, nv <37 U/ml), and were negative for Alpha-fetoprotein (AFP 3,89 ng/ml, nv <9 ng/ml) and Carcinoembryonic antigen (CEA 1,43 ng/ml, nv <5 ng/ml). CE-CT showed a complete opacification of the left hemithorax due to a massive pleural effusion with severe mediastinal shift and atelectasia of the left lung.
In the abdomen a large mass causing circumferential thickening of the gastric fundus with hyper- and homogeneous enhancing was found. The neoformation infiltrated the left diaphragmatic dome and the ipsilateral crus, causing a displacement of the spleen and ptosis of the left kidney (Figg. 1, 2).

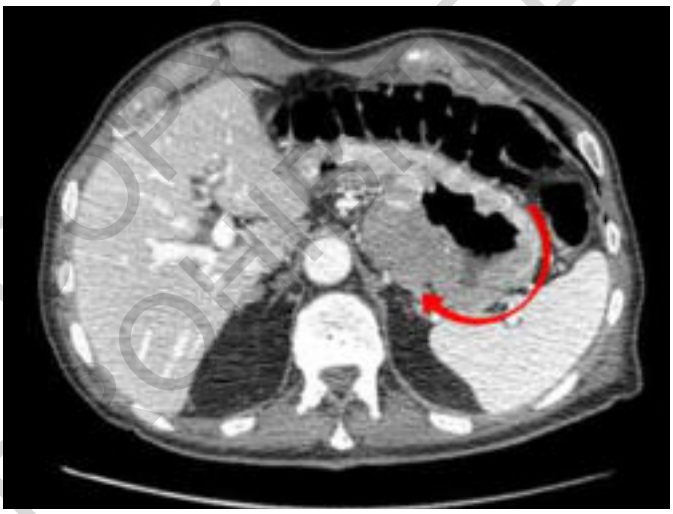

Fig. 1: Abdominal Contrast-enhanced CT scan. Axial image: the neoformation causes a circumferential thickening of the gastric fundus (arrow).

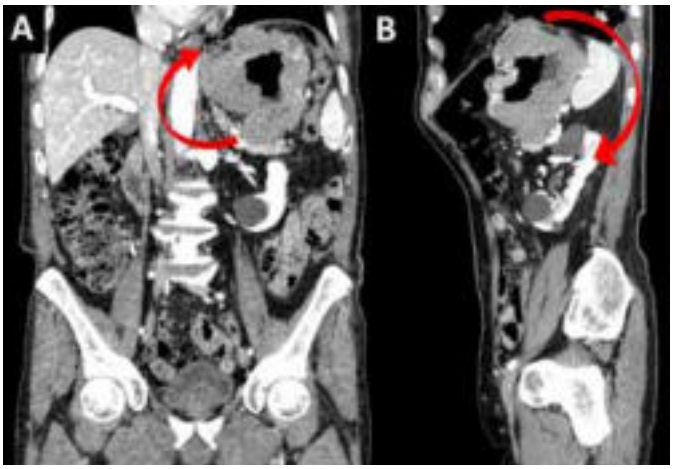

Fig. 2: Abdominal Contrast-enhanced CT scan. A) Coronal multiplanar reformatted image: gastric tumor thickness of 4cm, infiltrating the left diaphragmatic dome and the ipsilateral crus (arrow), takes contact with the splenic hilum. B) Sagittal multiplanar reformatted image: the mass effect caused by the tumor, in epigastric and left hypochondriac region, determinating postero-lateral dislocation of the spleen and ptosis of the ipsilateral kidney (arrow).

As first step a chest tube drainage in the left hemithorax was placed, and a cytology test of the yellow pleural effusion was performed but no atypical cells were found. Thoracoscopy was performed and multiple pleural biopsy specimens were taken for the histopathological examination (HE), that allow to make diagnosis of MPM. The patient underwent to thoracoscopic talc insufflation (TTI) for the left pleural effusion.

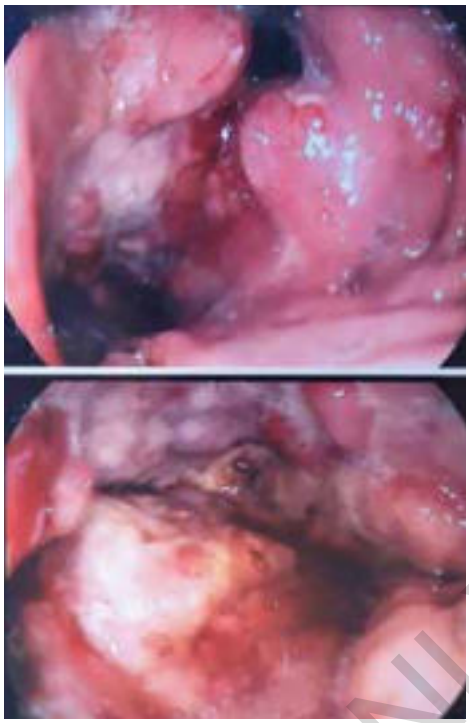

Fig. 3: Endoscopy: A large mass with everted margins at the gastric fundus, and widely ulcerated mucosa.

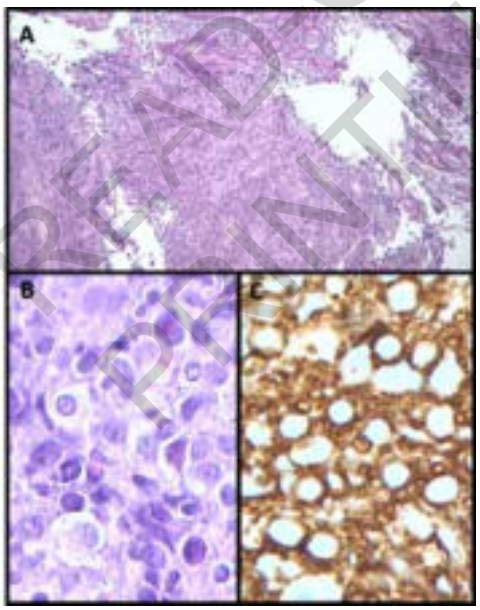

Fig. 4: Histology: H&E section shows an incisional endoscopic gastric biopsy involved by Burkitt Lymphoma (A20x; B40x). The normal glandular tissue is totally replaced by a star sky diffuse proliferation of medium-sized B cells CD20 positive (C40x).

An EGDS was performed and revealed a large, friable and widely ulcerated fundic mass protuding in the gastric lumen (Fig. 3). The EGDS did not show an active bleeding from the neoformation.

Four gastric biopsies of the mass were obtained, measuring from 5 to 3 mm and were buffered in 4% formaldehyde.

One HE staining was made (Fig. 4), showing gastric mucosa diffusely infiltrated by a lymphoproliferative disorder, with diffuse proliferation of medium-sized lymphoid cells with atypical nucleus and basophilic nucleoli. Numerous tingible body macrophages and necrosis areas were also found in the specimens. A little amount of uninvolved gastric tissue was identified. No intestinal neoplasia was found. Giemsa staining was negative for H. pylori.

Thirteen immunohistochemical staining were performed by Leica Bond-Max IHC stainer using 2 microns thickened positive charged microslides and Leica Biosystem Newcastle's antibodies: CD20 (L26), CD79a (JCB117),

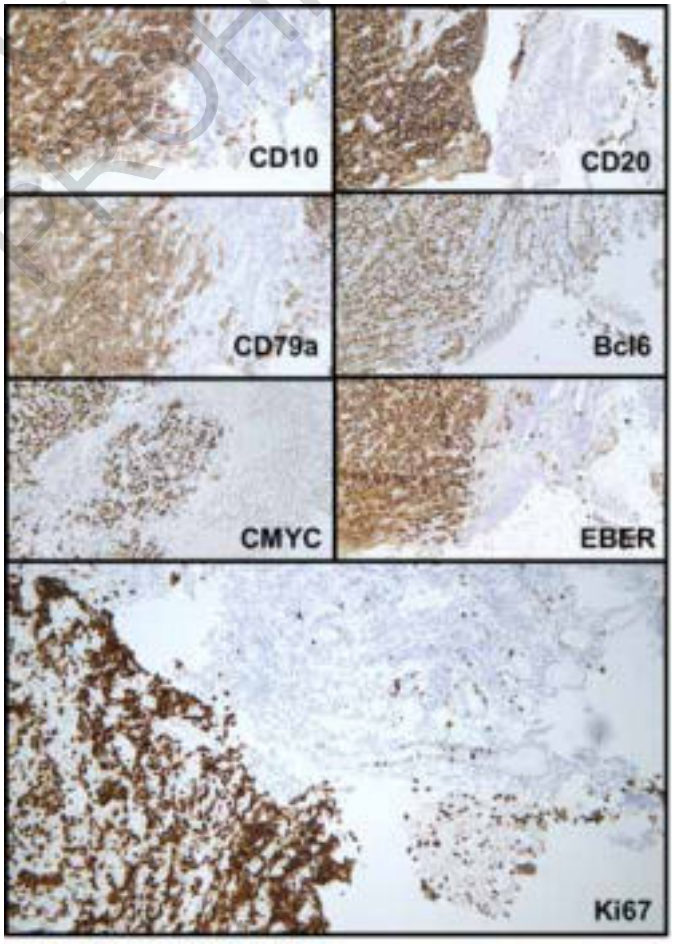

Fig. 5: Histology: Immunohistochemical panel of monoclonal antibodies showing positive and diffuse membrane expression for CD10, CD20 and CD79a, positive nuclei expression for Bcl6 (95%), CMYC (95%), EBER (95%) (20x) and Ki67 (95%) (10x).

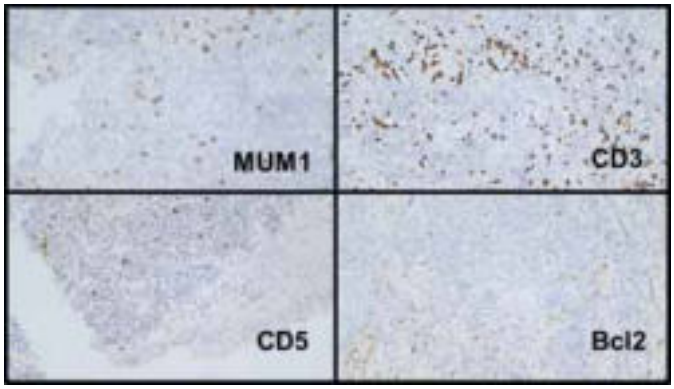

Fig. 6: Histology: Immunohistochemical panel of monoclonal antibodies showing negative expression with internal positive control for MUM1 (tumor cells negative, reactive B lymphocytes positive), CD3, CD5, Bcl2 (tumor cells negative, reactive T lymphocytes positive) (20x)

Bcl6 (LN22), Bcl2 (bcl-2/100/D5), CD10 (56C6), MUM1 (EAU32), CD21 (2G9), IgM (8H6), CMYC (Y69, 1:50 dilution*), TDT (SEN28), EBER Probe, CD5 (4C7), CD3 (LN10), Ki67 (MM1).
The lymphoproliferative disorder showed strong and diffuse membrane immunoreactivity for CD20, CD79a and CD10 confirming that it was a mature B cell neoplasm. Tumour cell nuclei were positive for Ki67 (95%), CMYC (95%), Bcl6 (95%), EBER (95%) (Fig. 5).
MUM1, CD3, CD5, Bcl2 were negative with internal positive control (Fig. 6). TDT, CD21, IgM were negative without control.
Histopathological diagnosis was: medium size B cell lymphoproliferative disorders same as BL.
After the TTI a surgical treatment of the gastric lesion was planned, due to the rapid growth and the high risk of bleeding as often observed in gastric BL.
Unfortunately, the patient died because of fatal cardiac arrhythmia after 15 days from TTI, before undergoing abdominal surgery.

Discussion

Single case reports and case series, including adults and children, represent the only literature currently available on PG BL.
In accordance with the available literature, in the reported case macroscopically on endoscopy the tumor appeared as an ulcerated large mass protuding in the gastric lumen [10-13], but the onset symptoms of our case, without an active bleeding from the gastric mass, make it a very singular case.
In fact, it was characterized by severe dyspnea up to respiratory failure, due to massive left pleural effusion and contralateral mediastinal fluttering, while CE-CT findings were instead negative for pleural thickening and positive for circumferential thickening of the gastric fundus. Malignant pleural effusion may be the first presentation of an unknown primary cancer [14], and it is a condition were surgical treatment has palliative purposes [15].
Based on the available literature, in management decisions no single strategy represents the treatment of choice, as several factors should be take into consideration, not least patient quality of life and symptoms control [16,17]. In our case TTI was the most indicated treatment to avoid respiratory distress caused by pleural effusion, which is characteristically massive and recurrent in MPM[6].
The clinical presentation of gastrointestinal lymphomas is usually associated with the tumor location. Abdominal pain is the onset symptom most frequently described in literature (85%) [10]. Acute presentation may be caused by perforation or obstruction with vomiting [10-12]. For PG BL the main primary manifestation is bleeding presented with melena or hematemesis [10-12], but PG BL may remain asymptomatic producing a scattered thickening of gastric wall until it becomes bulky, ulcerated and symptoms start to break out [13].
Among gastric lymphomas PG BL is one of the most aggressive sub-types of Non-Hodgkin's lymphoma (NHL) with growth fraction near to 100% and a doubling time of 25 hours [18]. The sporadic variant constitutes 30% of pediatric lymphomas but less than 1% of adult non HIV positive lymphomas and it usually appears in the ileocecal area [1]. Primary localization in stomach of BL is rarely reported in contrast with other types of NHL [10,19].
The role of both HIV and EBV infections in the etiology of BL have been confirmed in the past years, while still the link between PG BL and H pylori infection is controversial [3]. A small number of cases suggests the association between PG BL and H pylori infection [3,20,21], Baumgaertner I, et al in 2009 published a rare case of a 39 - year - old patient diagnosed with PG BL and positive for H pylori infection, who was successfully treated with chemotherapy along with the eradication of H pylori [20]. Although H pylori may be a risk factor for the development of PG BL, further studies and more data have to be collected the prove this relationship.
Biopsies obtained with EGDS allowed us to perform histopathological and immunohistochemical studies to achieve diagnosis. BL morphology shows diffuse infiltration of monomorphic, medium size lymphoid cells with basophilic cytoplasm, round nuclei with scattered chromatin and 3-4 distinct nucleoli. The tumor microscopy is characterized by the "starry sky" pattern. This typical appearence is due to spead tingible body-laden macrophages. BL displays a high proliferative and apoptotic activity [22]. Immunohistochemistry reveals the markers expressed by BL tumor cells such as CD19, CD20, CD10, CD79a, CD22, Tcl1 CD38, BCL6, surface IgM. The tumor cells are typically negative for CD5, TdT, BCL2 and Mum1 [23].

New monoclonal antibodies recognize c-myc protein expression which is localized in 88% of case in the nucleus and in the 12% is equally localized in the nucleus and cytoplasm of the tumor cells [24]. BL shows a very high proliferation activity and over 95% of the cells are positive for Ki67 [22].
PG BL is remarkably aggressive and the survival may not exceed a few weeks if untreated [13]. Fortunately BL shows remission with intensive combination chemotherapy and long-term survival is 40-80% [2,25,26].
The role of surgery is still controversial in literature. For early-stage disease in young patients chemotherapy is the first line of treatment, while for older patients standard treatment is represented by initial tumor cytoreduction followed by intense chemotherapy, particularly when the patient presents severe onset symptomps [4].

Conclusions

This is, to our knowledge, an unique case of clinical association between primary gastric Burkitt lymphoma and malignant pleural mesothelioma; the onset symptoms and radiological findings highlight the real challenge for the physicians to identify PG BL and MPM in early stage, especially in patients without the proved risk factors.

Riassunto

Il linfoma di Burkitt (BL) e il mesotelioma pleurico maligno (MPM) sono tumori rari con prognosi infausta e nella maggior parte dei pazienti è indicato solo il trattamento palliativo.
Il ruolo dell'infezione da HIV e da EBV nell'eziologia del BL sono stati confermati, mentre resta controversa l'associazione del BL a localizzazione gastrica con l'Helicobacter pylori.
Il BL è endemico in Africa e sporadico nel resto del mondo, la localizzazione primitiva nello stomaco (PG BL) è estremamente rara, fino al 2017 erano stati descritti solo 53 casi, ed è altamente aggressiva con una frazione di crescita tra le più alte tra i tumori maligni. La sintomatologia di esordio è costituita da vomito, dolore post-prandiale, sanguinamento acuto o cronico.
L'MPM è solitamente associato all'esposizione all'amianto e la dispnea dovuta a versamento pleurico è la manifestazione clinica tipica.
Finora in Letteratura non sono stati descritti casi caratterizzati dall'associazione del mesotelioma pleurico maligno con il linfoma gastrico primitivo di Burkitt.
Qui riportiamo il caso di un maschio caucasico di 80 anni, negativo per i comprovati fattori di rischio per LB e MPM, che si presentava alla nostra attenzione per un quadro di insufficienza respiratoria acuta da versamento pleurico massivo nell'emitorace sinistro, con sbandieramento mediastinico controlaterale. La tomografia computerizzata con mdc (CE-CT) mostrava una grossa massa causa di ispessimento circonferenziale del fondo gastrico, infiltrante la cupola diaframmatica sinistra e il pilatro omolaterale. All'esame endoscopico, il fondo gastrico appariva completamente occupato da una grossa massa ulcerata sporgente nel lume gastrico. L'esame istopatologico ed immunoistochimico dei campioni bioptici prelevati durante l'EGDS e la toracoscopia ha permesso di formulare la diagnosi di PG BL e MPM. Il paziente è stato sottoposto prima a posizionamento di drenaggio toracico per il versamento pleurico e poi a talcaggio pleurico toracoscopico nell'emitorace sinistro.
Per la rapida crescita e l'elevato rischio di sanguinamento veniva programmato il trattamento chirurgico della lesione gastrica, ma il paziente è deceduto a causa di un'aritmia cardiaca fatale, prima di sottoporsi all'intervento chirurgico addominale.
Questo case report mette in evidenza la vera sfida per i medici che è quella di identificare il MPM e il PG BL nella loro fase iniziale, specialmente nei pazienti senza i fattori di rischio comprovati. I sintomi di esordio ne fanno un caso molto singolare, caratterizzato da grave dispnea fino all'insufficienza respiratoria per versamento pleurico massivo sinistro e sbanderiamento mediastinico controlaterale, senza sanguinamento attivo dalla massa gastrica, mentre i reperti CE-TC erano invece negativi per ispessimento pleurico e positivo per ispessimento circonferenziale del fondo gastrico.

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