Pneumonectomy As A Salvage Therapy: A Rare Indication For A Gastric Malt Lymphoma Disseminated To The Lung

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Cite this article: Pneumonectomy As A Salvage Therapy: A Rare Indication For A Gastric Malt Lymphoma Disseminated To The Lung. Anna Pul and Crit Car Med.. 2018; 1(2): 01-04.

Submitted: 09 February 2018; **Approved:** 10 February 2018; **Published:** 12 Februay 2018

ABSTRACT

Gastric MALT lymphoma is a variety of B-cell Non Hodgkin Limphoma (NHL) which is linked , as a causative factor, to H. Pylori infection. In most of the cases, it is an indolent disease and H. Pylori eradication therapy has excellent clinical results and is accepted as the first line treatment. Sometimes MALT lymphoma can have an aggressive behaviour probably due to genetic acquired abnormalities like the translocation t(11;18)(q21;q21), which have been recently discovered.

This was probably the case of the patient we report here, who presented with an advanced disease infiltrating the stomach and disseminated to the right upper lobe of the lung. Medical therapy based on the combination of Chlorambucil and Rituximab, was unsuccessful in particular at the level of the lung where a disease progression was demonstrated.

A surgical approach was considered as the only mean to achieve a radical cure; because of the extensive neoplastic infiltration, the initial plan of a right upper lobectomy was not feasible. Instead, a right pneumonectomy was carried out as a "salvage procedure". This was a very unusual indication considered the high burden of complications associated to this risky operation and the advanced stage of the disease. Fortunately the post-operative course was uneventful and the patient, after 13 years since the operation, is still disease free. This unexpected success prompt our advice to consider pneumonectomy as a last resource in advanced stage MALT lymphomas resistant to traditional therapies.

Keyword: MALT lymphoma; Chemotherapy; Pneumonectomy

INTRODUCTION

Gastric MALT lymphoma is a variety of B-cell Non Hodgkin Limphoma (NHL) which is linked , as a causative factor, to H. Pylori infection. The H. Pylori positivity rate in the early stage of gastric MALT Lymphoma is approximately 90%1. Acquired genetic mutational abnormalities have been discovered to play a pathogenetic role and when present may identify some form of MALT lymphoma of particular aggressiveness. In most of the cases, it is an indolent neoplastic disease and H. Pylori eradication therapy has excellent clinical results and is accepted as the first line treatment2,3. For stage I and stage II MALT lymphoma resistant to eradication therapy or H. Pylori negative, radiotherapy has been accepted as the preferred organ-preserving local treatment modality4,5. A total of 97.8% of these cases respond to radiotherapy6. Gastric surgery is not indicated except in patients presenting with severe complications such as gastric perforation, hemorrhage or obstruction7 or in the patients that don't respond to eradication. The use of chemotherapy and immunotherapy has been reported in gastric MALT lymphoma of all stages; however it is the treatment of choice in the advanced staged of diesease. We describe a case of a patient with advanced disease (stage IV) involving the stomach and the right upper lobe. After several cycles of Chlorambucil and the anti CD20 antibody Rituximab, the gastric disease regressed while the lung infiltration progressed. The encroachment of the neoplasm into the main structure of the pulmonary hilum, hindered the initial plan of a right upper lobectomy. Instead, a right pneumonectomy was carried out as a "salvage procedure". This was a very unusual indication considered the high burden of complications associated by this risky operation; the exceptional aggressive behaviour of this particular case and the failed medical therapy were the only issues that supported our decision.

CASE REPORT

A 66 years old man was diagnosed with MALT lymphoma of the stomach in 2000. Diagnosis was reached by multiple endoscopic biopsies. The staging whole body CT casted the doubt of an extension of the neoplasm into the upper lobe of the right lung and this suspect was confirmed by trans-bronchial biopsy. The patient was counseled by the oncologists and because of the advanced stage he was treated with a total of six cycles of Chlorambucil combined with Rituximab. A complete remission of the disease was achieved in the stomach which remained disease-free up to 2005.

On the other hand, the tumor burden involving the right upper lobe remained stable up to 2004 but from 2005 a progression was observed. Indeed the chest X ray (fig 1) and CT scan (fig 2) revealed an enlargement of the lesion.

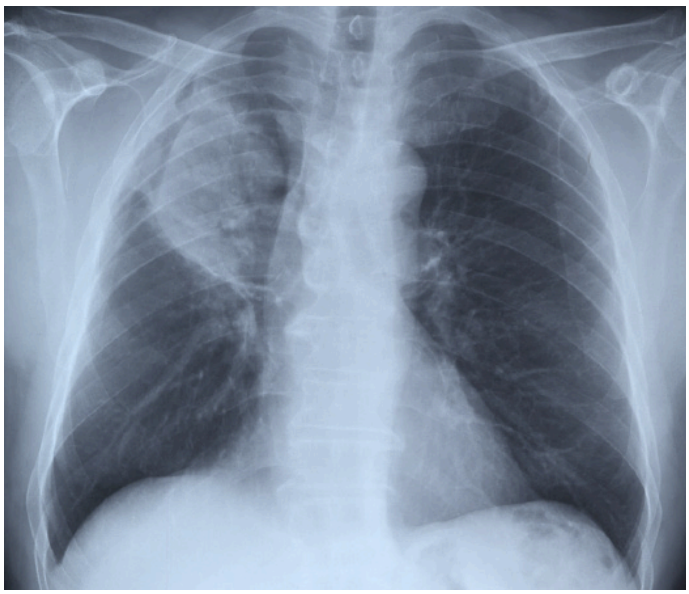

Figure 1. Gastric MALT lymphoma disseminated to the lung: the chest X ray shows a right upper lobe neoplastic opacity of increased size compared to (not shown) previous radiographs

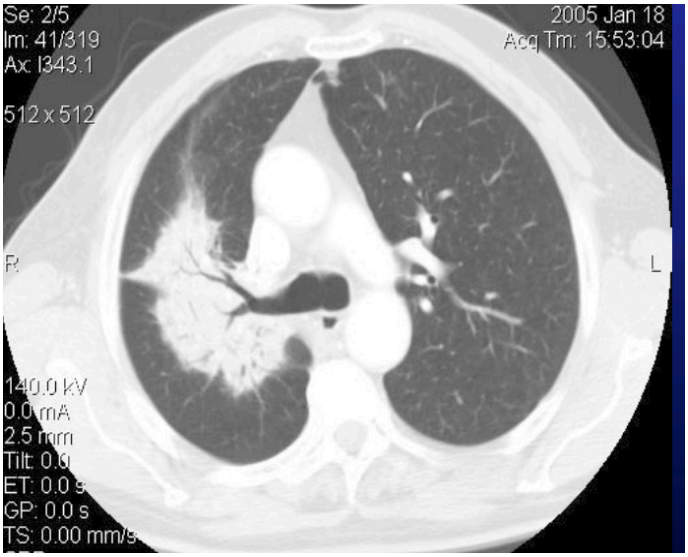

Figure 2. CT scan with lung windowing: almost complete opacification of the right upper lobe due to progression of MALT lymphoma of the upper right lobe

An abnormal 18FDG uptake was detected in the area of the upper right lobe when PET-TC was performed. Trans-bronchial biopsy confirmed persistent disease.

As a consequence, the oncologists referred the patient to our team of thoracic surgeons. At the preoperative evaluation the patient was found to have a good performance status; bearing in mind the relatively young age of the patient and the lack of response to medical therapy, we agreed on a surgical approach.

The preoperative imaging showed a narrowing of the right pulmonary artery, which was believed to be due to an external compression by the neoplastic mass. Therefore a right upper lobectomy was planned with a plasty of the right pulmonary artery.

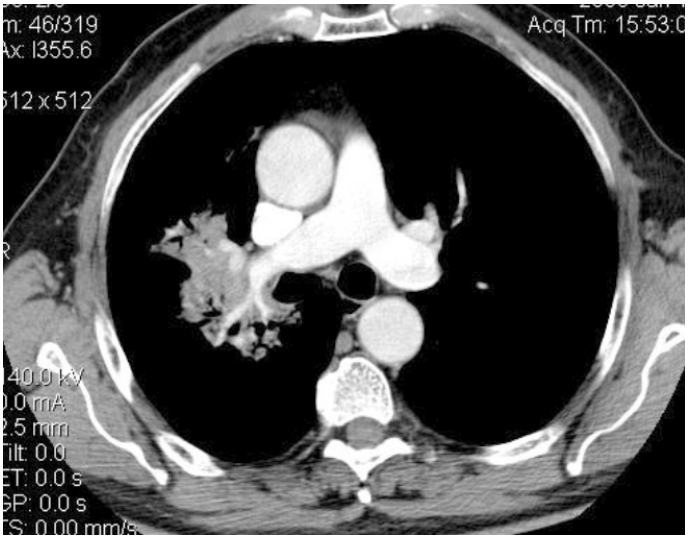

Figure 3. Contrast enhanced CT scan: stenosis of the right pulmonary artery at the level of the neoplasm

Unfortunately the intraoperative finding was that of an infiltration rather than a compression of the artery. Its plasty was deemed not technically feasible. The right upper lobectomy plan was abandoned and a right pneumonectomy was carried out as the only way to make the patient, at least locally, tumor free.

The postoperative course was uneventful and the patient was discharged in good health conditions on the 15th post-operative day, after a course of respiratory rehabilitation.

The pathological examination of the specimen reported a low grade MALT lymphoma of the lung with a tumor-free margin from the plane of resection of the artery, veins and bronchus of 1,5 cm (Figure4).

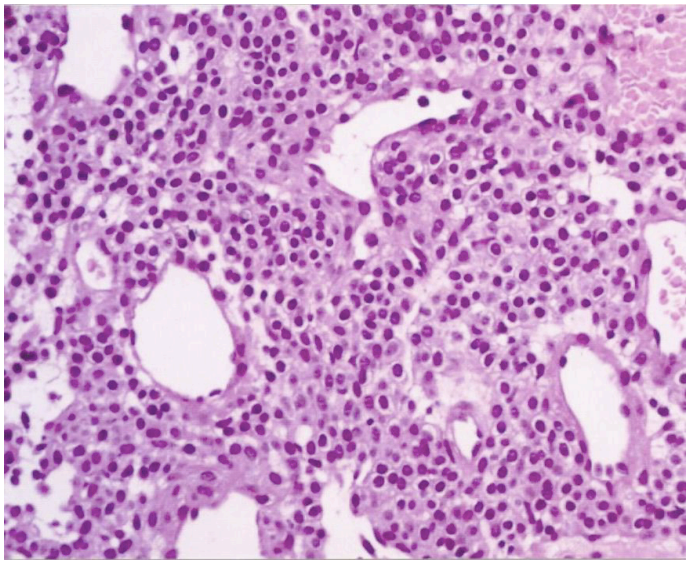

Figure 4. Hematoxylin-eosin stained histopathological examination of the right upper lobe specimen: the diffuse lymphomatous cell proliferation infiltrating the lung parenchyma is constituted by monomorfic lymphocytes with little atypia and often without a clear cytoplasm.

All the lymph nodes which had been harvested were tumor free. On immunohistochemical examination, the tumor was CD20+ CD5-, CD3-, CD 10-, CD 23- which is the usual phenotype of MALT lymphomas. Indeed the MALT lymphoma belongs to the B cell Non Hodgkin Lymphomas (NHL) which are characteristically CD 20 positive.

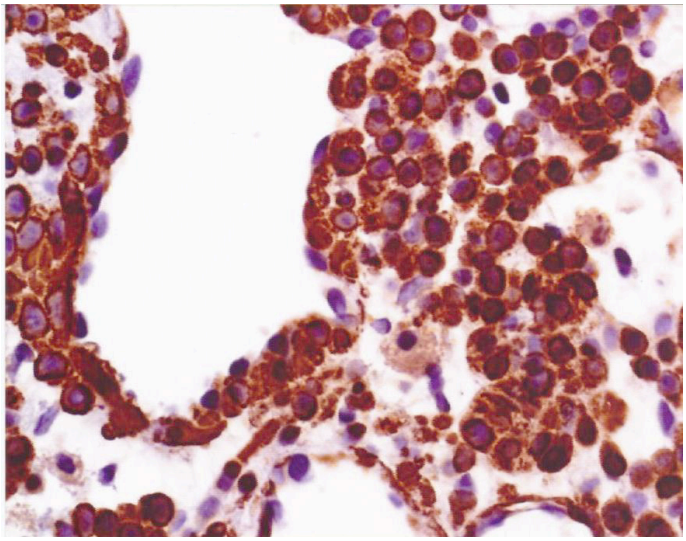

Figure 5. Immunohistochemical staining of the right upper lobe specimen: the lymphomatous cells are positive for CD 20, typical marker of B cells NHL

To date, about 13 years after operation, the patient is still on follow-up without evidence of disease recurrence in any district of the body.

DISCUSSION

Lymphoma deriving from the Mucosa Associated Lymphatic Tissue (MALT) was first described as a distinct pathological entity in 1983 by Isaacson and Wright8. Under the current WHO classification, it is classified as extranodal marginal zone lymphoma MALT type, and it is the third most common lymphoma type accounting for 8% of all Non Hodgkin Lymphomas (NHL)9. In 90 % of the cases, the origin of MALT gastric can be traced to chronic H. pylori infection. The chronic stimulus caused by this bacterium is responsible for the colonization of gastric mucosa by lymphatic cells, where they are physiologically absent, giving rise

independently from an antigenic stimulus. This represents a MALT lymphoma. At this stage these transformed lymphatic cells are still not able to spread beyond the site of inflammation. But with the accumulation of further mutational load, they become capable of systemic spread. This is when MALT lymphoma acquires a greater aggressiveness.

In recent years, progress has been made regarding MALT lymphoma pathogenesis. Three translocations, t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21) have been found to be associated with MALT lymphoma and the involved genes have been identified. Translocation t(11;18) results in a chimeric fusion between the API2 and MALT1 genes and is linked to gastric MALT lymphomas that do not respond to eradication of H. pylori. Translocations t(1;14) and t(14;18) deregulate BCL10 and MALT1 expression, respectively.

These mutated genes act as key regulatory factors of the cell cycle; all of them share the common oncogenic NF-κB pathway. NF-κB is a transcriptor factor that promotes cell survival10-12. So, in the end, the translocations t(11;18), t(1;14) and t(14;18) result in activation of NF-κB and in doing so enhance the survival of extranodal lymphoma cells13.

In light of their significance in biology these chromosome translocations, especially t(11;18) should be searched for, and this can be done by either fluorescent in situ hybridization or reverse-transcription polymerase chain reaction.

The median age of gastric MALT presentation is 63 yr, with a similar proportion of male and female patients. The majority of patients have an insidious onset of the disease and a very indolent course. The most common presenting symptoms are nonspecific like dyspepsia and epigastric discomfort. Classical B-symptoms are extremely rare. The most common gastric location is in the antrum, although multi-focal disease is seen in approximately in one third of cases. At upper endoscopy, erythema, erosions, or ulcerations are commonly seen whereas masses are rare.

For staging, either the Ann Arbor system (table 1) or the Lugano system for gastrointestinal lymphoma (table 2) can be used.

Table 1 Ann Arbor classification 1971

I	Involvement of one lymphatic area on one side of the diaphragm or of a single extralymphatic site (I_E)
II	Involvement of two or more lymphatic areas on one side of the diaphragm
III	Lymphatic involvement on both sides of the diaphragm
III_1	1: Lymph nodes in upper abdomen
III_2	2: Para-aortic, mesenteric, or pelvic lymph nodes enlarged
IV	Diffuse involvement of solid organs(s) or bone marrow and/or lymphatic involvement

A or B is indicated for all stages: A, no general symptoms; B, general symptoms (night sweats, fever, weight loss of >10%; E, localized extranodal involvement of a solid organ. X indicates a mass of >10 cm in diameter or a mediastinal mass less than one-third of the thoracic diameter is present.

Table 2 Lugano staging of Gastrointestinal Lymphomas

Stage I	Tumor confined to the gastrointestinal tract
Stage II	Tumor extending into the abdomen from the primary site
	II_1: Local node involvement (perigastric or perimesenteric)
	II2: Para-aortic or paracaval node involvement
	IIE: Penetration of serosa to involve adjacent organs or tissue
Stage IV	Disseminated disease or supradiaphragmatic lymph node involvement

No stage III defined.

Optimal treatment for gastric MALT lymphoma depends upon H. pylori status, disease stage, the presence of translocation like t(11;18), and evidence of large cell transformation. H. pylori eradication therapy is a worthy goal in all cases, and is probably the only therapy required in the majority of cases (75–80%)2,3. A common protocol for the eradication of H. pylori is the combination of omeprazole (20 mg twice a day), clarithromycin (500 mg twice a day), and amoxicillin (1 g twice a day) for 10–14 days. For patients who are allergic to penicillin, metronidazole (500 mg twice a day) can be used instead of amoxicillin. Eradication can be achieved in 85% of patients with both regimens. If the lymphoma does not regress after the eradication of H. pylori, a local irradiation (of 30 Gy) can lead to prolonged remissions4-6. Other options include watchful waiting, chemotherapy, and antibody-based (e.g. rituximab) approaches. The discovery that these non-respondent cases may have a translocation t(11;18) and a consequent constitutive activation of NF-κB, suggests that a targeted therapy, such as proteasome inhibition, when available, will be highly beneficial.

It is acknowledged that patients with advanced stages of disease should be treated like other indolent lymphoma. This was the case of our patient who presented with a stage IV disease according to either the Ann Arbor and Lugano staging. A treatment based on the alkylating agent Chlorambucil combined with the anti CD 20 monoclonal antibody Rituximab was chosen and administered for a total of six cycles. The use of Chlorambulcil combined with Rituximab is considered to be an active first-line therapy for patients with disseminated MALT lymphoma and to be effective irrespective of the t(11;18) status14.

A remission of the disease in the stomach was achieved as demonstrated by repeated endoscopic gastric biopsies. On the other hand, the lymphomatous involment of the right upper lobe remained stable up to 2004 and then progressed with an almost complete infiltration of the lobe.

Considered the goood performance status, young age and lack of response to medical therapy, we decided to perform an upper right lobectomy. The intraoperative finding of a neoplastic infiltration of the right pulmonary artery made our plan fall apart. A right pneumonectomy was then considered. Pneumonectomy is an highly demolitive procedure with a great impact on the patient physiology as it reduces the lung function of 50%. It is burdened by a wide range of complications some of which can also be life-threatening. For this reasons, nowadays indications for pneumonectomy are very limited and restricted to an highly selected group of patients. First of all, candidates must have a general good performace status; the extimated residual respiratory function should be permissible as predicted by a preoperative FEV1 and DL CO >80%. Moreover the procedure must be curative and not pallative; it's intuitive that there is no point to expose the patient to serious complications with to only aim of palliating rather then eradicating the neoplastic process. The criteria of good performance status and permissive respiratory function were met by our patient. From the oncological point of view, considering the advanced stage of the disease, we initially had some concerns. On the other hand, as the most effective medical therapy available had proved to be inefficacious, being this MALT lymphoma an aggressive rather than an indolent neoplasm, pneumonectomy appeared to be the last chance for the patient. Based on these considerations, right pneumonectomy was carried out as a salvage procedure. Fortunately none of the feared complications occurred and we were able to discharge the patient on the 15th post-operative day. After about 13 years since the operation, the patient is still in good health without any sign of recurrent disease.

CONCLUSION

Gastric MALT lymphomas are usually an indolent variety of B cell Non Hodgkin Lymphoma. Treatment is usually based on medical therapy and is successful in most cases. Sometimes this disease can have an aggressive behaviour and can present in an advanced stage with dissemination at different anatomical sites, as in our case. The successful treatment we report, demonstrates that, when

resistance to medical therapy is encountered, even a risky operation such as pneumonectomy, which is usually reserved for patients with localized and therefore curable disease, should be considered.

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