Multifocal early gastric cancer in a patient with atrophic gastritis and pernicious anemia

Tommaso Zurleni a,*, Michele Altomare b, Giovanni Serio b, Filippo Catalano c

a Department of General Surgery, ASST Valle Olo, Busto Arsizio Hospital, Italy
b Division of Anatomical Pathology, ASST Valle Olo, Busto Arsizio Hospital, Italy
c Emergency Endoscopy Unit, Borgo Trento, Verona, Italy

Abstract

INTRODUCTION: Pernicious anemia (PA) caused by vitamin B12 deficiency is associated with Autoimmune Metaplastic Atrophic Gastritis (AMAG). Patients with AMAG have threefold risk of the development of gastric cancer.

PRESENTATION OF CASE: We describe a case of a 66 year old man with a history of PA and atrophic antral-corpus gastritis. After endoscopic and chromoendoscopic evaluation the patient was treated with subtotal gastrectomy plus D2 lymphadenectomy. The tumor was diagnosed as Stage Ia: pT1a pN0 pM0 G2 with multiple foci of high grade dysplasia and intramucosal adenocarcinoma.

DISCUSSION: Multifocal Early Gastric Cancer can be a problem for minimally invasive treatment such as endoscopic excision.

Surgical management where it is not possible Endoscopic Mucosal Resection or Submucosal Resection (EMR/ESD) should include D1 or more type of lymphadenectomy because of the risk of unnodes metastases.

The chromoendoscopic evaluation may be helpful in the preoperative work-up and during the follow-up period.

CONCLUSION: Multidisciplinary approach is very important to reduce the under-treatment risk in multifocal early gastric cancer. Further studies will be needed to evaluate the safety of Subtotal vs Total Gastrectomy in this kind of disease.

© 2020 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

1.1. Autoimmune metaplastic atrophic gastritis (AMAG) and pernicious anemia (PA)

This case-report has been reported in line with the SCARE criteria [1].

AMAG is the result of antibody-mediated destruction of parietal cells that leads to long-term hematologic and neurologic consequences like iron deficiency anemia, Pernicious Anemia (PA), depression, irritability and psychosis [2].

The target antigens are the parietal cell H+·K+ ATPase, and Intrinsic Factor [3].

Historically, atrophic gastritis has been broadly divided into environmental and autoimmune etiologies [4]: the differences between Type A (AMAG) and Type B (HP Infection) gastritis, are summarized in Table 1.

Table 1: Type A (AMAG) and Type B (HP Infection) gastritis differences.

|               | Autoimmune | Infectious |
|---------------|------------|------------|
| Type          | A          | B          |
| Mechanism     | Autoantibodies against parietal cell antigens | Antrum |
| Distribution  | Body       | Antral     |
| Endoscopic Findings | Early disease: minimal findings | predominant atrophy; predominat atrophy (pseudopapillaps) |
|               | Late disease: body predominant atrophy (pseudopapillaps) | Epithelial dysplasia, adenomas, adenocarcinoma |
| Risk of malignancy | Type I endocrine tumor | Epithelial dysplasia and carcinoma |

Approximately 20–30% of patients with iron deficiency anemia without clinical evidence of blood loss have been reported to have AMAG [5]. PA is rarer and is a result of advanced AMAG. In a Swedish cohort study of more than 4000 patients with PA followed for 20 years, there was a 3-fold increased risk of gastric carcinoma and 13-fold increased risk of gastric carcinoid [6]. A more recent cohort study has reported an annual incidence rate of 1.36% person-year...
for gastric neoplastic lesion and 0.25% for gastric cancer (GC) [7]. Therefore, in the last years, reliable data are emerging that PA is linked to increased risk of Gastric Cancer [8]. According to these data some studies suggest that PA should be considered as independent risk factor able to target AMAG-patients subgroup with higher risk of neoplasm in Italy [9].

1.2. Multifocal early gastric cancer

Despite the reported declining incidence, GC is one of the most common causes of cancer mortality worldwide [10]. Different epidemiological trends in the intestinal type (InT) and diffuse type (DiT) Lauren histotypes have also been observed. The declining incidence of GC has been linked to the decreasing number of InT; on the other hand, the incidence of DiT is generally stable [11].

The term “Early Gastric Cancer” defined in 1971 by the Japanese Society of Gastroenterology and Endoscopy as carcinoma limited to gastric mucosa and/or submucosa, regardless of lymph node status, has continued to leave controversies over the years [12]. The percentage of lymph node metastases get from literature in EGC is still high: 11% for InT and 25.4% for DiT [13,14].

Fig. 1. Primary endoscopical evaluation.

A 0 T1 M type IIa of the distal antrum, 22 mm in size with white light high definition endoscopy (Photo 1), with Indigo Carmine dying (photo 2) and with a closed view by NBI (photo 3 and 4) highlighting two areas of infiltrative pattern.

Fig. 2. Chromoendoscopy control.
2. Presentation of case

We report a case of a 66-year old man with a history of 6 years of pernicious anemia and detection of atrophic antral-corpus gastritis. Antibodies against intrinsic factor and anti-parietal cell were positive.

During annual endoscopy control, it was found a small size distal lesion of the antral area of the stomach (Fig. 1).

Histological examination revealed a high-grade dysplasia (Hp neg with expression of Ki67 and P53 in more than 95% of cells).

Therefore the patient underwent chromoendoscopy and new biopsies of the superficial elevated pre-pyloric lesion of 22 mm (macroscopic evaluation: Type 0 T1m IIa) (Fig. 2).

Histological examination showed an intestinal type adenocarcinoma by Lauren. CT scan excluded distant metastases and lymphadenopathy, CEA: 3.8 and CA19.9: 4.

We decided to perform surgery after a multidisciplinary group discussion of the clinical case.

The patient underwent open subtotal gastrectomy with D2 type of lymphadenectomy (stat. n° 1-3-4-5-6-7-8(a,p)-9-11p-12(a,b,p)). Gastro-jejunal circular mechanical anastomosis with a Roux-en-Y type of reconstruction was performed (Fig. 3).

Neither intra nor post-operative complication occurred.

Histological examination revealed Multifocal Early Gastric Cancer infiltrating the muscularis mucosae; intestinal type by Lauren, tubular type by WHO moderately differentiated (Fig. 4).

Cytology on peritoneal washing was negative. 48 negative nodes were retrieved (pT1aN0M0 G2).

He had an uneventful recovery and he was discharged from the hospital 11 POD.

2.1. Follow-up

The patient underwent regular follow-up every 6 months by standard clinical and radiological controls and by endoscopic/chromoendoscopic evaluation. 5 years after surgery the patient is free from disease.
3. Discussion

Multifocality is a condition described in 0.8–22% of EGC [15] and can be a problem for minimally invasive treatment such as endoscopic excision. However, these techniques are not standardized as such in the Eastern hospital. In a recent study Suzuki et al. [16] evaluate the outcomes of EGC patients after non-curative ESD and define the necessity of following studies to identify patients who can undergo additional surgery, considering the risk of recurrence and metastasis.

An adequate preoperative investigation by endoscopy and chromoendoscopy and multidisciplinary approach are very important to plan the best therapeutic strategy in order to reduce the under-treatment risk, mostly considering that the sensitivity (62%) and specificity (65.7%) of CT-scan also in high grade tumors are still not trustworthy as showed in a recent study from Fukagawa et al. [17].

Interestingly, a recent study on genetic pathways of multiple intramucosal gastric cancer, demonstrated that synchronously developed multiple early gastric cancer shared the common feature of the MSI (microsatellite instability)/MSS (microsatellite stable) phenotype [18].

Regarding the prognosis, even if Kim et al. [19] concluded that synchronous multifocality of EGC does not increase the risk of lymph node metastases compared with solitary EGC, there are a lot of several studies in literature that identify multifocality as independent risk factor for developing Metachronous Gastric Cancer [20]. Moreover in a recent Cohort study Gertler analysed the prevalence of lymph node metastases in a group of 793 patients with early esophageal and gastric cancer, showing a lymph node involvement in 12.6%, with a different overall survival (OS) between the two groups (NO 89%; N+ 69%) [21].

Japanese Gastric Cancer Treatment guidelines (ver. 4) suggest in case of cT1N+ tumors a D2 lymphadenectomy, and D1 and D1+ lymphadenectomy in T1a tumors that do not meet criteria for EMR/ESD, and in all cT1bN0 [22]. Moreover Morgagni et al. [23] show how subtotal gastrectomy is strongly recommended despite of gastrectomy, when EMR/ESD approach is not faithful, for several reason: 1) secondary lesion are generally site in lower third near the main lesion; 2) secondary EGC sit in the upper third are rare; 3) subtotal gastrectomy have lower morbidity and mortality, a better quality of life and a similar survival rate compared to gastrectomy.

4. Conclusion

Multifocality in EGC can be a problem for minimally invasive treatment such as endoscopic excision. An adequate preoperative investigation by endoscopy, chromoendoscopy and multidisciplinary approach are very important to plan the best therapeutic strategy in order to reduce the under-treatment risk. Moreover, genetic and molecular features analysis could play a key role. Consistently with the high variability of OS between different endoscopic and surgical approaches in literature, further studies will be needed to evaluate the safety and feasibility of subtotal vs total gastrectomy in this kind of disease, considering that the use of laparoscopic total gastrectomy for gastric cancer remains controversial.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Sources of funding

No funding has been received for this study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from the patient prior to surgical procedure, figures used anonymous data.

Author contribution

Conception and design, acquisition, analysis and interpretation: T. Z., M. A., G. S., F. C.;

Writing and revising it critically: T. Z., M. A., G. S., F. C.; all authors contributed to this paper for the final approval of the final version.

Registration of research studies

NA.

Guarantor

Tommaso Zurleni, MD.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshy, A. Fowler, D.P. Orgill. For the SCARE Group. The SCARE 2018 statement: updating consensus Surgical Case Report (SCARE) guidelines, Int. J. Surg. 60 (2018) 132–136.
[2] A. Hunt, D. Harrington, S. Robinson, Vitamin B12 deficiency, BMJ 4 (349) (2014) e5226, http://dx.doi.org/10.1136/bmj.e5226, PMID: 25189324.
[3] Me Pittman, L. Voltaggio, F. Bhaire, Sa Robertson, Ea Montgomery, Autoimmune metaplastic atrophic gastritis: recognizing precursor lesion for appropriate patient evaluation, Am. J. Surg. Pathol. 39 (December) (2015) 1611–1620, http://dx.doi.org/10.1097/PAS.0000000000000481, PMID: 26291507.
[4] J.Y. Park, D. Lam-Himlin, R. Vemulapalli, Review of autoimmune metaplastic atrophic gastritis, Gastrointest. Endosc. 77 (2) (2013) 284–292, http://dx.doi.org/10.1016/j.gie.2012.09.033, PMID: 23199549.
[5] B. Annibale, G. Capurso, G. Delle Fave, The stomach and iron deficiency anemia: a forgotten link, Dig. Liver Dis. 35 (2003) 288–295, PMID: 12801042.
[6] A.W. Hsing, L.E. Hansson, J.K. McLaughlin, O. Nyren, W.J. Blot, A. Ekborg, J.F. Fraumeni Jr., Pernicious anemia and subsequent cancer. A population-based cohort study, Cancer 1 (71) (1993) 745–750, PMID: 8431855.
[7] E. Lahner, G. Esposito, E. Polizzi, F. Purchiaiorni, V.D. Corleto, E. Di Giulio, B. Annibale, Occurrence of gastric cancer and carcinoma in atrophic gastritis during prospective long-term follow-up, Scand. J. Gastroenterol. 50 (2015) 856–865, http://dx.doi.org/10.3109/00365521.2015.1010570.
[8] G. Murphy, S.M. Dawsey, E.A. Engels, W. Ricker, R. Parsons, A. Etemadi, S.W. Lin, C.C. Ahnert, N.D. Freedman, Cancer risk after Pernicious Anemia in the US elderly population, Clin. Gastroenterol. Hepatol. 13 (2015) 2282–2289, http://dx.doi.org/10.1016/j.cgh.2015.05.040, PMID: 26079040.
[9] E. Lahner, C. Hassan, G. Esposito, M. Carabotti, A. Zullo, M. Dinis-Ribeiro, B. Annibale, Cost of detecting gastric neoplasia by surveillance endoscopy in atrophic gastritis in Italy: a low risk country, Dig. Liver Dis. 49 (3) (2017) 291–296, http://dx.doi.org/10.1016/j.dld.2016.12.004, PMID: 28034664.
[10] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, CA Cancer J. Clin. 61 (2011) 69–90, http://dx.doi.org/10.3322/caac.20107, PMID: 21256855.
[11] H. Wu, J.A. Rusiecki, K. Zhu, J. Potter, S.S. Devesa, Stomach carcinoma incidence pattern in the United States by histologic type and anatomic site, Cancer Epidemiol. Biomarkers Prev. 18 (7) (2009) 1945–1952, http://dx.doi.org/10.1158/1055-9966.EPI-09-0250, PMID: 19531677.
[12] S. Abe, H. Yoshimura, S. Nagaoka, N. Monden, S. Kinugasa, N. Nagase, T. Nakamura, Long-term results of operation for carcinoma of the stomach in T1/T2 stages: critical evaluation of the concept of early carcinoma of the stomach, J. Am. Coll. Surg. 181 (5) (1995) 389–396, PMID: 7582205.
[13] A. Di Leo, D. Marrelli, F. Roviello, M. Bernini, A. Minicuzzi, S. Giacopuzzi, C. Pedrazzani, L.G. Baiocchi, G. de Manzoni, Lymph node involvement in gastric cancer for different tumor sites and T stage: Italian Research Group for Gastric Cancer (IRGCC) experience, J. Gastrointest. Surg. 11 (September (9)) (2007) 1146–1153, http://dx.doi.org/10.1007/s11605-006-0062-z, PMID: 17576611.

[14] M. Scartozzi, E. Galizia, L. Verdechcia, R. Berardi, F. Graziano, V. Catalano, P. Giordani, D. Mari, R.R. Silva, C. Marmorale, C. Zingaretti, S. Cascini, Lymphatic, blood vessel and perineural invasion identifies early-stage high-risk radically resected gastric cancer patients, Br. J. Cancer Suppl. 95 (2006) 445–449, http://dx.doi.org/10.1038/sj.bjc.6603286, PMID: 16880789.

[15] M. Kodama, G.E. Tur, N. Shozawa, K. Koyama, Clinicopathological features of multiple primary gastric carcinomas, J. Surg. Oncol. 62 (1996) 57–61, PMID: 8618403.

[16] H. Suzuki, I. Oda, S. Abe, M. Sekiguchi, S. Nonaka, S. Yoshinaga, Y. Saito, T. Fukagawa, H. Katai, Clinical outcomes of early gastric cancer patients after non-curative endoscopic submucosal dissection in a large consecutive patient series, Gastric Cancer 20 (July (4)) (2017) 679–689, http://dx.doi.org/10.1007/s10120-016-0651-z, Epub 2016 Oct 8, PMID: 27722825.

[17] T. Fukagawa, H. Katai, J. Mizusawa, K. Nakamura, T. Sano, M. Terashima, S. Ito, T. Yoshikawa, N. Fukushima, Y. Kawachi, T. Kinoshita, Y. Kimura, H. Yabuasaki, Y. Nishida, Y. Iwasaki, T. Yasuda, M. Sasaki, Stomach Cancer Study Group of the Japan Clinical Oncology Group, A prospective multi-institutional validity study to evaluate the accuracy of clinical diagnosis of pathological stage III gastric cancer (JCOG1302A), Gastric Cancer 21 (January (1)) (2017) 68–73, http://dx.doi.org/10.1007/s10120-017-0701-1, PMID: 28194522.

[18] A. Mizuguchi, A. Takai, T. Shimizu, et al., Genetic features of multicentric/multifocal intramucosal gastric carcinoma, Int. J. Cancer 143 (8) (2018) 1923–1934, http://dx.doi.org/10.1002/ijc.31578, PMID: 29717480.

[19] H.M. Kim, H.K. Kim, S.K. Lee, J.H. Cho, K.H. Pak, W.J. Hyung, S.H. Noh, C.B. Kim, Y.C. Lee, S.Y. Song, Y.H. Youn, Multifocality in Early Gastric Cancer does not increase the risk of lymph node metastasis in a single centre study, Ann. Surg. Oncol. 19 (April (4)) (2012) 1251–1256, http://dx.doi.org/10.1245/s10434-011-1917-z, Epub 2011 Oct 18, PMID: 22006373.

[20] S. Abe, I. Oda, T. Minagawa, M. Sekiguchi, S. Nonaka, H. Suzuki, S. Yoshinaga, A. Blatt, Y. Saito, Metachronous gastric cancer following curative endoscopic resection of early gastric cancer, Clin. Endosc. 51 (May (3)) (2017) 253–259, http://dx.doi.org/10.5946/ce.2017.104, Epub 2017 Sep PMID: 28920420.

[21] R. Gentler, H.J. Stein, T. Schuster, I.C. Rondak, H. Höfler, M. Feith, Prevalence and topography of lymph node metastases in early esophageal and gastric cancer, Ann. Surg. 259 (1) (2014) 96–101, http://dx.doi.org/10.1097/SLA.0000000000002339, PMID: 24096772.

[22] Japanese Gastric Cancer Association, Japanese gastric cancer treatment guidelines 2014 (ver.4), Gastric Cancer 20 (2017) 1–9, http://dx.doi.org/10.1007/s10120-016-0622-4, Epub 2016 Jun 2, PMID: 27342689.

[23] F. Morgagni, C. Marfisi, A. Gardini, D. Marrelli, L. Saragoni, F. Roviello, G. Vittimberga, D. Garcea, Italian Research Group for Gastric Cancer, Subtotal gastrectomy as treatment for distal multifocal early gastric cancer, J. Gastrointest. Surg. 13 (12) (2009) 2239–2244, http://dx.doi.org/10.1007/s11605-009-0971-9, Epub 2009 Aug 12, PMID: 19672668.

Open Access
This article is published Open Access at sciencedirect.com. It is distributed under the IJSCR Supplemental terms and conditions, which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.