RESEARCH ARTICLE

Lack of Any Relationship between ABO and Rh Blood Groups and Clinicopathological Features in Patients with Gastrointestinal Stromal Tumors: Turkish Oncology Group

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Abstract

Background: An association between the ABO blood group and the risk of certain malignancies, including pancreatic and gastric cancer, has been reported previously. However, it is unclear whether this association is valid for gastrointestinal stromal tumors (GIST). In this study, ABO blood groups and the Rh factor were investigated in a series of GIST cases. Material and Methods: In 162 patients with GIST, blood group and Rh factor were examined and compared with a control group of 3,022,883 healthy volunteer blood donors of the Turkish Red Crescent between 2004 and 2011. The relationship of blood groups with tumor size, mitotic activity, and age were also evaluated. Results: Overall, the ABO blood group and Rh factor distributions of the 162 patients with GIST were similar to those of the general population. There were no significant differences between both ABO blood types and Rh factor in terms of tumor size, mitotic activity, and age. Conclusion: This is the first study reported on this issue. In our study, we didn't find any relationship between GIST and ABO blood group and Rh factor. However further studies with larger number of patients are needed to establish the role of blood groups in this population.

Keywords: Gastrointestinal stromal tumor - ABO blood group - Rh factor - Turkey

Asian Pacific J Cancer Prev, **13**, 4129-4131

Introduction

Gastrointestinal stromal tumor (GIST)'s are the most common mesenchymal tumor of the gastrointestinal system. GISTs are different from other soft tissue tumors by histology, immunohistochemistry and molecular features (Corless et al., 2011). The term stromal tumors was introduced by Mazur and Clark in 1983 and GISTs were defined as a separate entity (Mazur and Clark, 1983). The discovery of activating KIT mutations in these tumors by Hirota et al. was an important milestone for the diagnosis and treatment of GIST (Hirota et al., 1998). Although it is difficult to determine GISTs frequency due to GISTs were underrepresented in the previous literature; an estimated incidence of these tumors is 1.5/100,000/year (Casali and Blay, 2010; Corless et al., 2011). The median age for GISTs is around 60 years. More than half of GISTs arise in the stomach and 25-30% of them in the small intestine. Although spindle cell and epithelioid cell are the most common types, approximately 10% of GISTs consist of a mixture of these two forms. Pathological diagnosis of GISTs relies on morphology and immunohistochemistry; a great proportion of GISTs (90-95%) are CD117 positive. Mutational analysis of KIT and platelet-derived growth factor A (PDGFRA) are helpful especially in patients with CD117 and DOG1 negative tumors. Also because of its predictive value for sensitivity for targeted therapy and prognostic value, mutational analysis is recommended (Heinrich et al., 2003: 2008; Debiec-Rychter et al., 2006; Casali and Blay, 2010). Tumor size, mitotic count and primary tumor site are considered major risk factor for prognosis. Standard treatment of the choice for the localized GIST is complete surgical excision. In locally advanced inoperable patients and metastatic patients, imatinib is standard treatment (Demetri et al., 2002; Blanke et al., 2008; Corless et al., 2011). After failure and discontinuation of imatinib, sunitinib has showed clinical benefit in patient with advanced GISTs (Demetri et al., 2006).

Blood group antigens are chemical components on the erythrocyte membrane but they are also expressed on a variety of epithelial cells including gastrointestinal

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mucosa. ABO blood group genes are mapped at the chromosome 9, in which the genetic alteration is common in many cancers (Hosoi, 2008). The correlations of ABO blood groups and Rh either with benign or malignant diseases has been observed for a long time. In 1953 Aird et al. reported such a relationship with gastric cancer (Aird et al., 1953). Recently a significant association between ABO blood groups and cancer of the pancreas was reported (Wolpin et al., 2009; Greer et al., 2010; Iodice et al., 2010). Additionally, genome wide association studies (GWAS) have identified the contribution of genetic variation in the ABO locus of 9q34 to pancreatic carcinogenesis (Amundadottir et al., 2009). Such a significant relationship hasn't been identified for GIST.

In this study, we aimed to investigate a relationship between ABO-Rh blood groups factor and GISTs and risk factor.

Materials and Methods

In 162 consecutive patients with GIST, blood group and Rh factor were examined. We excluded patients with a history of other cancer. All patients with pathologically confirmed GIST and had serologically determined blood group from medical oncology departments of Ankara University, Hacettepe University, Akdeniz University, Süleyman Demirel University, Ankara Numune Research and Educational Hospital, Dicle University, Dr. Abdurrahman Yurtarslan Ankara Oncology Research and Educational Hospital, and Karadeniz Tecnichal University were included. Patients classified according to antigen status as follow; O (blood group O) and nonO (group A, B, and AB); A (group A and AB) and nonA (group B and O); B (group B and AB) and nonB (group A and O). The distribution of blood groups of the patients were compared with a control group of healthy volunteer blood donors of 3.022.883 people between 01.01.2004 and 27.10.2011 obtained from Turkish Red Crescent (General Directorate of Blood Services, Science & Technological Research Directorate). The relationship of blood groups with tumor size, mitotic activity, and age were also evaluated in the patients group.

Statistical analysis was carried out using the Statistical Package for the Social Sciences 11.5 for Windows (SPSS, Inc, Chicago, IL, USA). Mean±standard deviation [median (minimum-maximum)] for continuous variables and frequency (percent) for categorical data were used as descriptive statistics. A chi-square test was used to detect differences in proportions. Kruskal-Wallis analysis and Mann-Whitney U test were used to determine the independent group differences in terms of continuous variables. All tests were two-tailed and a p value of less than 0.05 was considered significant.

Results

Overall, the ABO blood group distribution of the 162 patients with GISTs was similar to that of the Turkish general population (Table 1). While the percentages of patients with A, B, AB and O blood groups were 42.2%, 16.3%, 7.6% and 33.9, those of controls were 44.4%, 14.2%, 9.3% and 32.1%, respectively (p=0.71). There were no statistically significant differences between patients and controls regarding the distribution of A vs. nonA (p=0.32), B vs. nonB (p=0.75) and O vs non-O (p=0.63). Also 87.7% of both patients and controls were Rh+ (p=0.98).

Table 1. ABO Blood Groups and Rh Factor Distribution of Patients with Gist and Control Group

	GIST Group		Control Group	
	n	%	n	%
A+	67	41.4	1,121,702	37.1
A-	5	3.1	154,330	5.1
B+	20	12.3	434,143	14.3
B-	3	1.9	59,626	2
AB+	14	8.6	200,972	6.7
AB-	1	0.6	28,582	1
O+	41	25.3	894,210	29.5
O-	11	6.8	129,318	4.3
Total	162	100	3,022,883	100

*GIST: gastrointestinal stromal tumor

Table 2. ABO Blood Groups According to Clinicopathologic Characteristics

Characteristics	ABO BLOOD GROUPS				
	A	B	AB	O	p value
Sex					
Female n (%)	30 (41.7)	7 (30.4)	6 (40.0)	16 (30.8)	0.57
Male n (%)	42 (58.3)	16 (69.6)	9 (60)	36 (69.2)	
Age (year)*	55.6±13 [55 (27-82)]	58.2±13.5 [63 (34-86)]	51.6±13.1 [50 (31-75)]	54.4±12.5 [54 (25-81)]	0.43
Tumor size (cm)*	11.0±7.1 [9 (1-35]	8.8±5.6 [7.5 (1-20)]	7.3±1.3 [7 (6-9)]	8.6±5.6 [7.5 (1-27)]	0.36
Number of mitoses per 50 HPF**	8 (1-94)	5 (1-140)	2 (1-17)	5 (0-65)	0.11

*Age and tumor size were described as mean±standard deviation [median (minimum-maximum), **Number of mitoses was described as median (minimum-maximum), cm: centimeter; HPF: high-power fields.

In patient group, the median age was 55 (range: 25-86) years. Hundred and three (63.6%) of the 162 patients were male. More than half of tumors arised from stomach (49 patients, 30.2%) and small intestine (45 patients, 27.8%). The median tumor size was 8 cm (range: 1-35 cm). The median number of mitoses per 50 high-power fields (HPF) was 6 (minimum-maximum: 0-140). There were no statistically significant differences between the blood groups (A, B, AB and 0) regarding age (p=0.43), mitotic activity (p=0.11), tumor size (p=0.36), primary tumor site (p=NA) and sex (p=0.57). Moreover no statistically significant differences were found between the Rh status and tumor size, mitotic activity, primary tumor site and age.

Discussion

The human ABO genes are located on chromosome 9q34.1 – q34.2. There are three main allele forms, A, B, and O (Hosoi, 2008). The primary gene products are glycosyltransferases. ABO blood groups are determined by carbohydrate moieties, A and B antigens, on the

extracellular surface of the red blood cell membranes and anti-A or anti-B antibodies in the serum. However ABO antigens are also expressed on the surface of many other cells, like epithelial cells. Alterations on the cell surface carbohydrate structures such as ABH blood group antigens can change the cell-cell and cell-extracellular matrix interactions that might be important for tumor development (Dall'olio, 1996). Possible associations between ABO blood group and the risk of some epithelial malignancies, including pancreatic cancer and gastric cancer have been reported previously (Aird et al., 1953; Amundadottir et al., 2009; Wolpin et al., 2009; Greer et al., 2010; Iodice et al., 2010;). A relationship between gastric cancer and ABO blood groups was reported by Aird et al. in the 1950s. The frequency of blood group A was greater and O was lower in patients with gastric cancer than normal population. The distribution of blood group A and O was 44.8% and 44.5% in patient with gastric cancer and 39.8% and 48.6% in control group respectively (Aird et al., 1953). Pancreatic cancer is another cancer that relationship of ABO blood group was reported (Amundadottir et al., 2009; Wolpin et al., 2009; Greer et al., 2010; Iodice et al., 2010). Wolpin et al. reported that risk of pancreatic cancer was higher in patient with non-O blood group (A, B, and AB) than O. They observed highest risk for participants with blood group B (Wolpin et al., 2009). Although Greer et al reported that frequency of blood group O was lower in patient with pancreatic cancer, in their study there was limited number of patients with blood group B and the frequency of blood group A was significantly higher than normal population (Greer et al., 2010). Likewise Iodice et al. reported that O blood group was associated with a 47% risk reduction of pancreatic cancer but they didn't observe significant differences in the distribution of A versus non-A in patient with gastric cancer (Iodice et al., 2010). However population based cohort study of Edgren et al. has confirmed the association between blood group A and gastric cancer (Edgren et al., 2010). Despite data about cancer and ABO blood groups no consistent relationship between ABO blood type and GISTs has been reported so far. In the present study we also found a similar distribution of blood group types in patients with GIST and general population.

To our knowledge, this is the first analysis of ABO blood group in patient with GIST. In our study, we didn't find any relationship between GIST and clinicopathological feature of GISTs and ABO blood group and Rh factor. Another study with larger number of patients may clarify the role of blood groups in this population.

Acknowledgements

We are indebted to Armağan Aksoy, M.D. and the Turkish Red Crescent (Türk Kızılayı [General Directorate of Blood Services, Science & Technological Research Directorate]) and Önder Arslan, M.D. and Ankara University Medical School Blood Center for their help. Conflict of interest, the authors declared that there are no potential conflicts of interest, neither financial nor of other nature, to disclose.

References

Aird I, Bentall HH, Roberts JA (1953). A relationship between cancer of stomach and the abo blood groups. *Br Med J*, **1**, 799-801.

Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al (2009). Genome-wide association study identifies variants in the abo locus associated with susceptibility to pancreatic cancer. *Nat Genet*, **41**, 986-90.

Blanke CD, Rankin C, Demetri GD, et al (2008). Phase iii randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol*, **26**, 626-32.

Casali PG, Blay JY (2010). Gastrointestinal stromal tumours: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, **21**, 98-102.

Corless CL, Barnett CM, Heinrich MC (2011). Gastrointestinal stromal tumours: Origin and molecular oncology. *Nat Rev Cancer*, **11**, 865-78.

Dall'olio F (1996). Protein glycosylation in cancer biology: An overview. *Clin Mol Pathol*, **49**, 126-35.

Debiec-Rychter M, Sciot R, Le Cesne A, et al (2006). Kit mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer*, **42**, 1093-103.

Demetri GD, van Oosterom AT, Garrett CR, et al (2006). Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. *Lancet*, **368**, 1329-38.

Demetri GD, von Mehren M, Blanke CD, et al (2002). Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*, **347**, 472-80.

Edgren G, Hjalgrim H, Rostgaard K, et al (2010). Risk of gastric cancer and peptic ulcers in relation to abo blood type: a cohort study. *Am J Epidemiol*, **172**, 1280-5.

Greer JB, Yazer MH, Raval JS, et al (2010). Significant association between abo blood group and pancreatic cancer. *World J Gastroenterol*, **16**, 5588-91.

Heinrich MC, Corless CL, Demetri GD, et al (2003). Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol*, **21**, 4342-9.

Heinrich MC, Owzar K, Corless CL, et al (2008). Correlation of kinase genotype and clinical outcome in the north american intergroup phase iii trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: Calgb 150105 study by cancer and leukemia group b and southwest oncology group. *J Clin Oncol*, **26**, 5360-7.

Hirota S, Isozaki K, Moriyama Y, et al (1998). Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science*, **279**, 577-80.

Hosoi E (2008). Biological and clinical aspects of abo blood group system. *J Med Invest*, **55**, 174-82.

Iodice S, Maisonneuve P, Botteri E, et al (2010). Abo blood group and cancer. *Eur J Cancer*, **46**, 3345-50.

Mazur MT, Clark HB (1983). Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol*, **7**, 507-19.

Wolpin BM, Chan AT, Hartge P, et al (2009). Abo blood group and the risk of pancreatic cancer. *J Natl Cancer Inst*, **101**, 424-31.