Journal of Gastrointestinal & Digestive System

Canda MS, J Gastroint Dig Syst 2014, 4:5
DOI: 10.4172/2161-069X.1000231

Review Article Open Access

Gastrointestinal Stromal Tumors, Interstitial Cells of Cajal and their Nomenclature

Mehmet Serefettin Canda*

Medical Faculty, Dokuz Eylül University Medical School Department of Pathology, Turkey

***Corresponding author: Mehmet Serefettin Canda**, Dokuz Eylül University Medical School Department of Pathology, Balcova-Izmir, Turkey, Tel: 0905337083135; Fax: 0902322777274; E-mail: serafettin.canda@deu.edu.tr

Received date: Sep 11, 2014, **Accepted date:** Oct 22, 2014, **Published date:** Oct 27, 2014

Abstract

Currently, gastrointestinal stromal tumors (GIST) have been emphasized considerably in the literature. Following the date of the description of interstitial cells of Cajal (ICC) by Santiago Ramon y Cajal in the late 19th century, this issue has been very popular. Lately, discovery of the association of GISTs with c-Kit mutations in their development, and the significance of drugs such as imatinib, that inhibit c-Kit mutations in their treatment, has increased the interest of researchers. Our aim is to review the nomenclature about ICC and GISTs in the light of literature, to discuss the definition of GIST, which is a heterogeneous, pleomorphic tumor, in its historical progression and in the light of new data, and to suggest the naming these tumors as “tumor of Cajal”, “”Cajal tumor” or “Cajal cell tumor” instead.

Keywords: Santiago Ramon y Cajal; Gastrointestinal stromal tumor (GIST); Gastrointestinal autonomic nerve tumor (GANT); Gastrointestinal pacemaker cell tumor (GIPACT); Interstitial cells of Cajal (ICC); Interstitial cells of Cajal Tumor (ICCT); Ic-Kit mutation; Tumor of Cajal; Cajal tumor; Cajal cell tumor

Introduction

Towards the end of the 19th century, Ramon y Cajal (May 1, 1842 – October 17, 1934) described the cells now referred to as the “Cajal interstitial cells” or the “Interstitial cells of Cajal” (ICC) [1,2] Santiago Ramon y Cajal, a Spanish neurohistology expert, working with a light microscope in 1892 described the specialized “interstitial neurons” found in the tubular gastrointestinal tract. His complet work on the nervous system brought him the Nobel Prize in medicine in 1906, which he shared with Camillo Golgi [3,4].

Clinical and histological researches conducted since then have established the importance of ICC.

The current developments in researches concerned gastrointestinal stromal tumor (GIST) research have enhanced the importance of the ICC. Current findings indicate that ICC cells are found outside the gastrointestinal system as well, and extragastrointestinal stromal tumors (EGIST) are encountered [4].

We are aim at placing an emphasis on the significance of ICC in GIST, at reviewing and making suggestions about the nomenclature of these tumors based on historical and current knowledge.

Interstitial Cells of Cajal

The interstitial cells of Cajal (ICC) are “pacemaker” cells that are found in the muscle layer of the intestinal wall. They facilitate the communication between enteric nervous system and the muscle layer of the intestinal wall, thereby ensuring the peristalsis (rhythmic and coordinated contraction) of the intestinal wall [5].

C-Kit positive ICC, are found in the gastrointestinal tractus, both around the myenteric plexus and in the muscularis propria. Contrary to what Cajal postulated, they are not neuronal in origin but mesodermal in origin [6].

The uncertainty regarding ICC lasted for approximately 100 years until it was finally understood that GIST arose from ICC or ICC like cells (interstitial cells of Cajal-like precursor) [7].

For the development and survival of ICC, a tyrosine kinase receptor protein called c-Kit (CD177) is required (8). Consequently, a c-Kit mutation leads to the development of GIST [8].

Gastrointestinal Stromal Tumor

GISTs develop from ICC or their stem cell-like precursors. GISTs are non-epithelial tumors. They are the most commonly seen mesenchymal tumors that constitute approximately 2% of the tumors seen in the gastrointestinal tractus [9-14].

GISTs constitute nearly 60% of cases in the stomach (40%-60%), 30% of cases (20%-40%) in the small intestines (ileum and jejunum), less than 5% of cases in the duodenum, and less than 1% of cases in the mouth [14]. They are seen mostly in adults after 40 years of age, and they have a peak in the 6th and 7th decade of life [15-17].

A small percentage (%5) of GISTs forms extra gastrointestinal masses in the omentum, mesenteries, retroperitoneum, rectovaginal septum and undefined abdominal sites [17-18] and very rarely in vulva [19]. These tumors are occasionally designated as extragastrointestinal stromal tumors (EGIST) [17].

Histological Differential Diagnosis and Clinical Implications

Histologically GISTs are usually spindle cell tumors. It is striking to note that they have previously been misdiagnosed as leiomyoma, leiomyoblastoma or leiomyosarcoma for many times. Though rare,

epithelioid and pleomorphic variants have also been described [14,20,21]. The term GIST was first proposed by Mazur and Clark in 1983 [22]. In 1984, Herrera defined gastrointestinal autonomic nerve tumors (GANT) as "plexosarcoma" [23-25]. In 1998, Kindblom defined gastrointestinal "pacemaker" cell tumors as "gastrointestinal pacemaker cell tumors-GIPACT" [12].

Immunohistochemical, GIST cells are stained positively with c-Kit (95%) and CD34 [10,11]. These tumors can show a weak positivity with some other mesenchymal tumor markers as well. For this reason other mesenchymal, neuronal and neuroendocrine tumors should be in the differential diagnoses from c-Kit negative GISTs. In these cases kinase C theta and DOG1 may be helpful [26].

Currently although tyrosine kinase inhibitors such as imatinib mesylate and sunitinib malate, which arrests the growth of GISTs by inhibiting c-Kit offer a good prognosis, they are resistant to secondary c-Kit mutations. In addition, these drugs are ineffective in GISTs arising from the stem cells of the gastrointestinal tractus. Therefore it is important to differentiate tumor stem cells immunohistochemically [26].

On the other hand, isolating ICC stem cells and investigating their signal pathways along with the reason why they do not respond to drugs such as imatinib mesylate and sunitinib malate is a path with many hurdles. However, in recent years researches regarding differentiation of ICC stem cells and their identification have increased considerably. Tamas and Ordog have shown that ICC stem cells, in comparison to mature ICC have lower concentrations of c-Kit (less expression). It is for this reason that GISTs developing from ICC stem cells do not respond to drugs such as imatinib mesylate and sunitinib malate [27].

ICCs are mesodermal in origin [22]. ICC and smooth muscle cells arise from common precursor cells that express c-Kit (tyrosine kinase receptor). The fully developed smooth muscle cells do not express c-Kit, whereas ICCs continue to express c-Kit. For this reason c-Kit is a specific determinant for ICCs [28,29].

Recent studies have shown that some ICCs develop into ventrally migrating neural tubes [30].

GIST Subtypes and their Antigenic Properties

Immunohistological, GISTs are categorized as c-Kit-mutant GIST (80%), PDGFRA-mutant GIST (5-8%), "wild-type" GIST (12-15%), c-Kit-negative GIST (5%) and GIST syndromes. In adults GIST syndromes are neurofibromatosis type 1 (NF1), the Carney triad (epithelioid GIST of the stomach, extra-adrenal paraganglioma, pulmonary chondroma), familial GISTs (2008), multiple GISTs, and secondary GISTs (secondary mutations due to imatinib treatment). During imatinib treatment generally in areas I and II of c-Kit or PDGFRA tyrosine kinase, due to imatinib resistant secondary mutations, acquired drug resistance, as metastatic diseases may be seen in such cases [31].

Conclusion

GISTs are the most commonly seen mesenchymal tumors of the gastrointestinal tractus, they constitute approximately 2% of all gastrointestinal tumors [14]. Although initially it was believed that GISTs arose from Cajal cells or smooth muscle cells, and that they were mesodermal in origin, today it is understood that they arise from multipotent mesenchymal stem cells [31-33].

Currently GISTs are tumors that are appear extensively in the scientific literature, and there are suggestions as to their nomenclature. For example Mazur and Clark defined GISTs as a group of non-epithelial heterogeneous stromal neoplasms [22].

In 1984 Herrera defined gastrointestinal autonomic nervous system tumors (GANT) as "plexosarcoma" (23-25). Recently Kindblom et al. in the light of electron microscope findings defined gastrointestinal pacemaker cell tumors (GIPACT) as "pacemaker tumors" [12] (Table I).

Year	Authors	Nomenclature	Reference No
1983	Mazur and Clark	GIST	(22)
1984	Herrera	GANT "plexosarcoma"	(23-25)
1998	Kindblom	GIPACT "pacemaker tumor."	(12)
1999	Sircar K	ICCT	(34)
2002	Rhatigan	Cajal tumors, Cajal cell tumors	**(35 / (35)**

Table 1: Nomenclature about GISTs with related referances; Abbreviations: GIST, gastrointestinal stromal tumor; GANT, gastrointestinal autonomic nervous system tumor; GIPACT, gastrointestinal pacemaker cell tumor

In 1998, Hirota published that GISTs show c-Kit mutations (c-Kit protein, CD117) [10,11]. This finding led to the determination of the origin of this tumor and by using chemotherapeutic agents that inhibit c-Kit (CD 117), such as imatinib mesylate (a tyrosine kinase inhibitor for the c-Kit protein), good results were managed to be able to were obtained.

In conclusion, GISTs are pleomorphic, heterogeneous, mesodermal stromal tumors of the gastrointestinal tract. The interstitial cells of Cajal (ICC) called, they were first identified in the late 19th century by Ramon y Cajal [1-4]. In light of the advances in the field and the emergence of different viewpoints [33], I believe the time to change the nomenclature of these tumors has come, and instead of GIST calling them Cajal tumors, tumors of Cajal or Cajal cell tumors would be more inclusive and appropriate, previously as indicated in 1999 by Sircar K (ICC tumor/ICCT) [34] and in 2002 by Rhatigan (Cajal tumors, Cajal cell tumors) [35].

In light of the advances in the field and the emergence of different viewpoints [33], I believe the time to change the nomenclature of these tumors has come, and instead of GIST calling them Cajal tumors, tumors of Cajal or Cajal cell tumors would be more inclusive and appropriate, as indicated in 1999 by Sircar K (ICC tumor/ICCT) and in 2002 by Rhatigan RM (Cajal tumors, Cajal cell tumors) previously [34,35].

I aim to make a scientifically and histologically contribution to the discussion of these topics. Currently, GIST definition is really widely used in the medical field, in the light of scientific developments, it will be more appropriate to use both Cajal tumor (tumor cells of Cajal) and GIST together, in order to avoid any confusion. In my opinion, there will still be necessary some new perspectives and discussions about this issue.

Therefore, for the clarification of this issue, there is a need for new concepts and new proposals. As a result, the definition of Cajal cell tumor (Cajal tumor) is more specific definition than that of GIST, in

terms of histology and science though GIST is accepted as a general definition.

References

1. Piotrowska AP, Solari V, Rolle U, Puri P (2004). Interstitial cells of Cajal in the human normal urinary bladder and in the bladder of patients with mega cystis-microcolon intestinal hypoperistalsis syndrome. BJU Int 94: 143-146.
2. Sanders KM, Ward SM (2006). Interstitial cells of Cajal: a new perspective on smooth muscle function J Physiol 576: 721-726.
3. The Nobel Prize in Physiology or Medicine 1906. Nobelprize.org. 31 Jan 2013. http://www.nobelprize.org/nobel prizes/ medicine/laureates/1906/
4. Padhi S, Sarangi R, Mallick S (2013) Pancreatic extragastrointestinal stromal tumors, interstitial Cajal like cells, and telocytes. JOP 14: 1-14.
5. Sanders KM, Koh SD, Ward SM (2006) Interstitial cells of cajal as pacemakers in the gastrointestinal tract. Annu Rev Physiol 68: 307-343.
6. Komuro T, Seki K, Horiguchi K (1999) Ultrastructural characterization of the interstitial cells of Cajal. Arch Histol Cytol 62: 295-316.
7. Sanders KM, Ward SM (2006) Interstitial cells of Cajal: a new perspective on smooth muscle function. J Physiol 576: 721-726.
8. Miettinen M, Lasota J (2005) KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation. Appl Immunohistochem Mol Morphol 13: 205-220.
9. Laurini JA, Carter JE (2010) Gastrointestinal stromal tumors: a review of the literature. Arch Pathol Lab Med 134: 134-141.
10. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, et al. (1998) Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279: 577-580.
11. Andtbacka RH, Ng CS, Scaife CL, Cormier JN, Hunt KK, et al. (2007) Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 14: 14-24.
12. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM (1998). Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 152: 1259-1269.
13. Stamatakos M, Douzinas E, Stefanaki C, Safioleas P, Polyzou E, et al. (2009) Gastrointestinal stromal tumor. World J Surg Oncol 7: 61.
14. Joensuu H (2006) Gastrointestinal stromal tumor (GIST). Ann Oncol 17 Suppl 10: x280-286.
15. Sandrasegaran K, Rajesh A, Rushing DA, Rydberg J, Akisik FM, et al. (2005) Gastrointestinal stromal tumors: CT and MRI findings. Eur Radiol 15: 1407-1414.
16. Miettinen M, Kopczynski J, Makhlouf HR, Sarlomo-Rikala M, Gyorffy H, et al. (2003) Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol 27: 625-641.
17. Miettinen M, Sobin LH,Lasota J. (2009) Gastrointestinal stromal tumors presenting as omental masses-a clinicopathologic analysis of 95 cases. Am J Surg Pathol 33: 1267-1275.
18. Divakaran J, Chander B (2012) Primary extra-gastrointestinal stromal tumor of the omentum. J Cancer Res Ther 8: 433-435.
19. Fukuda T, Sumi T, Nakano Y, Morishita M, Nobeyama H, et al. (2011) Extragastrointestinal stromal tumor originating from the vulva. Oncol Lett 2: 797-799.
20. Canda MS, Saraoaylu S, Saayol A, Bakarh H, Astarcaylu K, et al. (1995) Association of gastiric leiomyoblastoma and uterus myomatosis: an anusual case report. Turkish Journal of Cancer 25:172-175.
21. Canda AE, Ozsoy Y, Nalbant OA, Sagol O (2008) Gastrointestinal stromal tumor of the stomach with lymph node metastasis. World J Surg Oncol 6: 97.
22. Mazur MT, Clark HB (1983) Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 7: 507-519.
23. Herrera GA, Pinto de Moraes H, Grizzle WE, Han SG (1984) Malignant small bowel neoplasm of enteric plexus derivation (plexosarcoma). Light and electron microscopic study confirming the origin of the neoplasm. Dig Dis Sci 29: 275-284.
24. Herrera GA (1985) Small bowel neoplasm. Dig Dis Sci 30: 698.
25. Herrera GA, Cerezo L, Jones JE, Sack J, Grizzle WE, et al. (1989) Gastrointestinal autonomic nerve tumors: 'Plexosarcomas'. Am J Surg Pathol 17: 887-897.
26. Kang GH, Srivastava A, Kim YE, Park HJ, Park CK, et al. (2011) DOG1 and PKC-Î¸ are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors. Mod Pathol 24: 866-875.
27. Lorincz A, Redelman D, Horváth VJ, Bardsley MR, Chen H, et al. (2008) Progenitors of interstitial cells of cajal in the postnatal murine stomach. Gastroenterology 134: 1083-1093.
28. Hirst GD, Ward SM (2003) Interstitial cells: involvement in rhythmicity and neural control of gut smooth muscle. J Physiol 550: 337-346.
29. Torihashi S, Ward SM, Sanders KM (1997) Development of c-Kit-positive cells and the onset of electrical rhythmicity in murine small intestine. Gastroenterology 112: 144-155.
30. Sohal GS, Ali MM, Farooqui FA (2002) A second source of precursor cells for the developing enteric nervous system and interstitial cells of Cajal. Int J Dev Neurosci 20: 619-626.
31. Corless CL, Heinrich MC (2008) Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev Pathol 3: 557-586.
32. Stamatakos M, Douzinas E, Stefanaki C, Safioleas P, Polyzou E, et al. (2009) Gastrointestinal stromal tumor. World J Surg Oncol 7: 61.
33. Min KW, Leabu M (2006) Interstitial cells of Cajal (ICC) and gastrointestinal stromal tumor (GIST): facts, speculations, and myths. J Cell Mol Med 10: 995-1013.
34. Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, et al. (1999) Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol 23: 377-389.
35. Rhatigan RM (2002) GIST nomenclature. Hum Pathol 33: 1242.