IJPSR (2013), Vol. 4, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 February, 2013; received in revised form, 22 March, 2013; accepted, 20 May, 2013

CLINICOPATHOLOGICAL STUDY OF 115 CASES OF GLIOBLASTOMA MULTIFORME WITH SPECIAL REFERENCE TO GLIOSARCOMA

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Keywords:

Glioblastoma Multiforme (GBM), Gliosarcoma (GS), Immunohistochemistry (IHC), Haematoxylin and Eosin (H & E), Microscopically (M/E)

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QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(6).2384-92

Article can be accessed online on: www.ijpsr.com

ABSTRACT:

Background: Glioblastoma Multiforme is the commonest of all astrocytomas. It accounts for 12-15% of all intracranial neoplasm and 50-60% of all astrocytic tumors. Most common site of occurrence is cerebrum and age incidence is highest in fifth and sixth decade. Gliosarcoma constitutes 2% of all brain tumors, 5% of all astrocytomas and 8% of anaplastic astrocytomas. The cell of origin of sarcomatous component has not been fully established.

Aim: The purpose of our study is to evaluate histopathological features of GBM in detail, in relation to the age, sex and site of occurrence, in Ganga Ram Hospital, during a period of 10 years and also to find out the relative frequency of Gliosarcoma among glial tumors. Particular emphasis is on to evaluate the nature of glial as well as mesenchymal component and their relationship in Gliosarcoma with the help of immunohistochemistry.

Materials: Total of 115 cases of Glioblastoma multiforme were studied histopathologically in detail, with some clinical corelation in Sir Ganga Ram hospital. 13 cases of Gliosarcomas, diagnosed morphologically as well as with the use of special immunohistochemical stains for sarcomatoid elements. This is a prospective as well as retrospective study between January 1995 and December 2005 Method: All the cases were examined M/E for cellularity, pleomorphism, mitosis, necrosis, haemorrhage, vascularity including endothelial proliferation and sarcomatous component. These features were graded subjectively into mild (+), moderate (++) and severe (+++). All the suspected sarcoma cases were confirmed by reticulin stain and then these Gliosarcomas were further analyzed with 5 more IHC stains like GFAP, ASMA, Desmin, FactorVIIIR/Ag and p53.

Results: All the Glioblastoma Multiforme cases were common in fifth and sixth decade with male to female ratio of 2.38:1. Common site of occurrence was cerebrum and the common clinical symptoms were headache, mental change and vomiting. Microvascular proliferation and gemistiocytic cell population was seen in variable amount in all cases. Gliosarcoma were found to be common in males of 51-70yrs. Based on p53 staining, primary Gliosarcoma were found to be more common than the secondary ones. Analysis of the pattern of reticulin stain supports the vascular origin of Gliosarcoma. Factor VIII and ASMA positivity in sarcomatous area supports their origin from smooth muscle cell of vessel wall.

INTRODUCTION: GBM may occur de-novo (primary glioblastoma) or more often as progression from a preexisting astrocytoma (secondary glioblastoma). GBM and its variants correspond to WHO grade IV [1]. GBM is an undifferentiated highly cellular tumor with marked pleomorphism,

hyperchromasia and frequent mitosis. Necrosis and endothelial proliferation are two important criteria's for diagnosis. Endothelial proliferation is believed to be due to angiogenic factors produced by the tumor cells themselves.

Gliosarcoma is a biphasic neoplasm composed of GBM admixed with a sarcomatous component that is presumed to arise from a malignant transformation of the hyperplastic vascular elements [2]. The glial component is usually astrocytic in nature showing morphologic features of glioblastoma or anaplastic astrocytoma and sarcomatous component is commonly a fibrosarcoma. However, it has rarely been found to be in the form of smooth and skeletal muscle, bone and cartilage [3, 4, 5, 6, 7].

Feigin and Gross 1955 8 suggested that the sarcomatous component in GS develops as a result of neoplastic transformation in markedly hyperplastic blood vessels, commonly found in GBM. Sarcomatous change has been considered to be from endothelial, pericytes or undifferentiated mesenchymal cells. This view has been generally accepted and progressive transformation of sarcoma from blood vessels has been recorded in humans [8, 9, 10)] as well as in an experimental study, reported by Green and Harvey 1968 [11].

Endothelial markers such as factor VIII related antigen [12] and *Ulex europeaus* agglutinin (UEA-1) have been found in the sarcomatous tumor cells [10]. However, some studies in recent years have suggested that the sarcomatous component is the result of progressive loss of GFAP in some parts of glioma along with the acquisition of sarcomatous phenotype [13, 14]. These studies are indicative of origin of both the components from glial cells; the sarcomatous change representing a phenotypic transformation of glioblastoma cells [15].

Kepes *et al*., [6] reported chondroid cells in astrocytomas resulting from metaplastic change, since they were positive for GFAP. In glioblastoma, metaplastic epithelial cell formation has been reported [16, 17]. Biernat *et al*., [18] found an identical alteration of p53 gene in both components of GS and suggested origin of both components from a common progenitor. In an *in-situ* hybridization study, an identical alteration in chromosome 10 and 17 has been observed in both the glial and mesenchymal components of GS [19].

The possibility that the saromatous component arises from phenotypic change of glioblastoma cells has also been suggested in a recent study by Reis *et al* [20]. So far with all these studies, the cell of origin of sarcomatous component has not been fully established and the origin of sarcoma element is still in controversy.

MATERIAL: This prospective as well as retrospective study was carried out in the Department of Histopathology, Sir Ganga Ram Hospital, New Delhi. A total of 115 patients were included, during a period of January 1995 to December 2005. January 1995 to July 2005 constitutes retrospective component and August 2005 to December 2005 constitutes prospective component.

METHOD: Formalin-fixed paraffin-embedded tissue sections were routinely stained with Hematoxylin and Eosin stain. Reticulin and Masson Trichome were also used, as and when required. All the GM cases were examined microscopically for cellularity, pleomorphism, mitosis, necrosis, hemorrhage, vascularity including endothelial proliferation and sarcomatous component and are graded subjectively into (+) mild (++) moderate and (+++) severe. Out of all the GBM, Gliosarcoma proven with reticulin were analyzed with 5 more immuno-histochemical stains like GFAP, ASMA, Desmin, Factor VIIIR/Ag and p53. The intensity of these stain were graded subjectively as (+) mild (++) moderate and severe (+++). IHC staining was based on UltraTech Streptavidin-Biotin System.

Observations related with GBM: Analysis of the cases is depicted below:-

Age and Sex distribution of GBM (Table 1): Maximum number of cases were found in the age group of 51-60 years, whereas minimum no were seen in 71-80 years of age group. The youngest patient was 6 year old while the oldest one was 72 year old. GBM was found to be more common in males (81 out of 115 cases) with male to female ratio of 2.38:1. The co-relation of age with sex in patients with GBM shows that the most common mean age in females was in between 51-60 years whereas males were affected more often at earlier age than that of females i.e. the mean age group of 41-50 years. Second most common age group in males was the same as that of females i.e. i in between 51-60 years of age.

TABLE 1: DISTRIBUTION OF CASES OF GBM ACCORDING TO SEX AND CORRELATION OF AGE AT DIAGNOSIS

AGE	SEX		%age	
	Female	Male	Female	Male
<20	2	3	5.88%	3.70%
21-30	2	6	5.88%	7.40%
31-40	4	12	11.76%	14.81%
41-50	6	24	17.64%	29.62%
51-60	12	23	35.59%	28.39%
61-70	7	12	20.58%	14.81%
71-80	1	1	2.94%	1.23%
Total	**34**	**81**	**100%**	**100%**

Location of GBM: The commonest site of GBM was frontal region, followed by temporal and then temporo-parietal region (24%, 19% & 13%). Other commoner sites affected were parietal, fronto-parietal, thalamic, parieto-occipital and fronto-temporal. But there were some sites that were rarely affected. These include occipital region, IV ventrical, III ventrical, paracentric region and cerebellum. Only one or two cases were seen in these rare sites.

Clinical features of GBM: The three common symptoms were headache, muscle weakness and vomiting (42%, 40% & 22% respectively). All others symptoms were seizures, altered sensorium, nausea, speech disturbances, vision defects, urinary incontinence, memory loss and facial nerve palsy.

Microscopic features of GBM: Morphological analysis included the degree of cellularity, pleomorphism, mitosis, amount of necrosis and vascular proliferation. Most of GBM were moderately or highly cellular. Low cellularity was seen in less than one fourth of the cases. Pleomorphism of the tumor cells correlated well with the degree of the cellularity. Most of the tumors were showing cells of different sizes and shapes. A small number of tumors were composed generally of uniform-looking cells.

Necrosis was present in mild to moderate amount in most of the cases. Extensive areas of geographical necrosis were seen in comparatively less number of cases. Some of the tumors were showing pallisading of tumor cells around areas of necrosis. Variable numbers of mitotic figures were seen in almost all cases. There was varying degree of vascular proliferation in these cases of GBM, as is seen in the **table 2**. Vascular proliferation was in the form of focal increase in 33.91% of cases, moderate increase in vascularity was seen in 40.00% of cases and widespread and diffuse increase was seen in 26.08% of cases.

Five cases of glioblastoma showed glomeruloid body formation. Variable numbers of gemistiocytic cells were seen in 20 of the 115 cases of glioblastomas.

TABLE 2: OBSERVATION RELATED WITH 4 IMPORTANT MICROSCOPIC FEATURES OF 115 CASES OF GBM

MICROSCOPIC FEATURES	+	++	+++
Cellularity	20 (17.39%)	62 (53.91%)	33(28.69%)
Pleomorphism	22 (19.13%)	60 (52.17%)	33(28.69%)
Necrosis	41 (35.65%)	47 (40.86%)	27 (23.47%)
Vascularity	39(33.91%)	46(40.00%)	30(26.08%)

Observations related with Gliosarcomas: Gliosarcoma constituted 11.3% of all cases of GBM. The clinical features including the age, sex and site of involvement are given in **table 3**. All the cases were showing spindle cell element suggesting the presence of sarcomatous components in GBM. Reticulin stain was done initially to confirm the presence of sarcomatous component in GBM.

The immuno-histochemical stains were employed for further analysis of the gliosarcomatous areas. They included GFAP, ASMA, Desmin, Factor VIII and p53. These 13 cases were analyzed separately.

Age and Sex distribution of GS: It was noted that GS was prevalent in elderly patient's i.e.in age group of 51-70 years. This correlates closely with the mean age of GBM patients.

The youngest patient of GS was a 20 year old female and the oldest patient was also a female of 72years. Out of 13 cases of GS 8 were found in male and 5 in female. So GS were more common in male as that of GBM, but the M: F ratio of sex distribution was less in GS as compared to GBM. The ratio in GS was 1.6:1, compare to 2.38:1 in GBM.

Location of GS: Site commonly affected by GS was temporal, frontal and parietal which matches with the sites affected by GBM. Although the most frequent site affected in patients with GBM was frontal, the occurrence of GS was commonest in the temporal lobe. One case of GS was seen in cerebellum involving a large area and extending along the meninges. Cerebellum is an unusual site for this tumor.

Clinical features of GS: Combination of sign and symptoms were present in all cases, muscle weakness (39%) was the main presenting symptom in most cases of GS. Other clinical features were headache, difficulty in speech, sudden hemiphasia, altered sensorium, loss of appetite, facial palsy and seizures.

Microscopic features (Table 3): Microscopic examination of GS showed sarcomatous tissue intermingled with or in different foci of pre-existing glioblastomatous tissues. The spindle-shaped cells were seen in relation with the blood vessels in most of the cases. Some of the cases on H&E showed the origin of spindle shaped cells from the wall of the blood vessels. Most of gliosarcomas were hypercellular.

TABLE 3: OBSERVATIONS RELATED WITH IMPORTANT MICROSCOPIC FEATURES SEEN IN 13 CASES OF GS

Microscopic Features	+	++	+++
Cellularity	0	4	9
Pleomorphism	1	7	5
Mitosis	5	8	-
Vascularity	1	7	5
Endothelial proliferation	5	4	4

Cases with low cellularity were very few. Pleomorphism was moderate to mark in most cases. Number of mitotic figures, in contrast to the high grade of tumors in general, was less in most of the GS, though abnormal form of mitosis was frequently seen. Although necrosis was seen in all the cases, as per WHO criteria of grade IV astrocytomas, the degree was very variable in areas showing GS and it was graded as mild to moderate, when present. No significant hemorrhage was seen in most of the cases. Vascular proliferation was moderate to mark in most cases and on examination of H&E stained sections, endothelial proliferation was demonstrable in significant amount in the majority of cases. One of the case, among the 13 GSs showed mucoid differentiation.

IHC Staining of GS: In all the 13 cases, the diagnosis of GS was confirmed initially by the presence of rich reticulin network. The reticulin stain revealed a continuous spectrum in which large reticulin-rich areas were merging with reticulin-poor areas. Out of 13 GS, in 9, sarcomatous areas occupied a large part of tumor. In many of them sarcomatous tissue appeared to be originating from the wall of the blood vessels and forming intimate network of reticulin around them. The reticulin-rich area corresponds to the sarcomatous area consisting of spindle cells in H&E stained section. Such areas were examined in detail on H&E as well as following five IHC stains done on each case of GS.

The stains were GFAP, ASMA, Desmin, Factor VIIIR/Ag and p53. The results of staining were graded subjectively according to the degree of positivity as +, ++ and +++. The results of these six stains are given in table 4.

TABLE 4: IHC STAINING OF GS FOR GFAP, RETICULIN, ASMA, DESMIN, FACTOR VIIIR/Ag AND p53

CASE	Retic	GFAP	ASMA	Desmin	Factor VIII	P53
1	+++	+	++	na	+	-ve
2	+++	-ve	+++	na	-ve	-ve
3	++	++	+	-ve	+++	+++
4	+++	+	-ve	na	-ve	-ve
5	+++	++	-ve	na	++	-ve
6	+++	++	+	na	-ve	+
7	+	+	+	na	+	-ve
8	+++	+	+	na	++	-ve
9	+++	+	-ve	na	+++	-ve
10	+++	++	+++	-ve	+++	++
11	+	+	+	na	+	-ve
12	+	+	na	-ve	+++	-ve
13	+	-ve	-ve	na	-ve	-ve

(na= not applicable)

Comparative analyses of all these stain were done in relation with particular area showing positivity for reticulin.

Sections stained for GFAP showed variable degree of positivity in all the 13 cases. The area which was positive for reticulin showed no or fewer GFAP positive cell, intermingling with the GFAP negative cell. The glioblastomatous area was showing moderate to severe degree of positivity.

ASMA showed positivity in 8 cases, 4 were negative and in one case the stain was not done. In these also only 2 of the cases showed strong positivity and 6 cases were of mild to moderate degree of positivity. These areas (ASMA positive) on H&E showed spindle shaped cells and there positivity with ASMA strongly confirms the leiomyomatous nature in 2 of the 13 cases.

Factor VIIIR/Ag was done in all the 13 cases and it showed strong (+++) positivity in 4 of the 13 cases in the selected (so called sarcomatous) area. Moderate degree (++) positivity was seen in 2 cases and 3 cases were mildly (+) positive. Positive cells were seen around the vessel wall and suggest their origin from the wall of the vessel and were seen to be extending into the sarcomatous area. This suggests participation of endothelial cells in the origin of sarcoma in GBM.

To evaluate the nature of GS, whether it is primary or secondary, p53 stain was done. It was found to be positive in only 3 cases. Out of which 1 was (+) positive, and other was (++) positive. Only one case was (+++) positive. This suggests the secondary nature of the GS in this case only.

Desmin was done in three cases suspected to be of leiomyomatous nature on H&E but it turned out negative in all these three cases.

ANALYSIS OF RESULTS:

GBM: In the present study, the overall incidence of GBM as well as the sex and age incidence was found to be similar to those reported in the literature [1, 21]. Frankel and German [22] reviewed 219 cases of GBM with regard to natural history, pathology, diagnostic methods and treatment. He found sex incidence of 58% and 42%, in males and females respectively and age incidence was highest in the fifth and sixth decade in his case series. Many other subsequent studies also showed similar picture. In the present study we also found GBM more common in males and the age incidence was highest in fifth and sixth decade.

Glioblastoma is most commonly localized in cerebral hemisphere as also seen in a series of 987 cases of glioblastomas from the University Hospital Zurich. The same was found in our study too. In their series the common sites in cerebrum were temporal, parietal and frontal in deceasing order of frequency. We found frontal, temporal and parietal in decreasing order of frequency.

The common presenting clinical picture in GBM in our series was also similar to that is recorded in the literature. There was no difference found in the sign and symptoms of the patients of GBM in our study compared to those reported by Frankle and German [22]. The three most common sign and symptoms found in our study were headache, mental change and vomiting.

In the present study, out of 115 cases of glioblastoma multiforme, 20 were showing gemistiocytes, some of them also showing giant cell formation. Presence of gemistiocytes in GBM is very well described in literature. The gemistiocytic astrocytomas are regarded as WHO grade of II or III lesions and they tend to rapidly progress to glioblastoma [23]. Presence of gemistiocytes in a glioblastoma favors its origin from gemistiocytic astrocytoma, differentiating in a glioblastoma. Microscopic examination of glioblastomas generally showed a very variable pattern including variable degree of cellularity and the cellular pleomorphism in the past literature.

In the present series also, the morphological picture, including the degree of cellularity was extremely variable. Most of the cases were moderately cellular. Tumor cells were pleomorphic in almost all the cases, but a few were composed of primarily monotonous population of cells. Necrosis was present in all of the cases.

Microvascular proliferation of varying degree was present and many of them showed glomeruloid body formation also. Thus there was no striking difference found in histopathology, including the cellular and tissue pattern of GBM in our case series and those recorded earlier.

GS: As has been noted earlier, gliosarcoma as a separate entity was recorded for the first time by Strobe in 1895 [24]. However, it took a long time before its acceptance in the literature. The entity was firmly established after a detailed study reported by Feigin and Gross [25] in which they described the occurrence of sarcoma in association with GBM. Subsequently, many such cases have been reported in literature.

In various series, the incidence of GS has been reported to vary from 2% to 8% (9). In the present series, GS accounted for 11.3% of all GBM cases (13/115). This appears to be higher in comparison with other reported series.

However, age and sex incidence and the site of occurrence of GS were closely similar to the other reported cases.

Study of Morantz and colleague described that great percentage of patients with GS were older than 60 years of age and in our study most of the patients were in the age group of 51 to 70 years. This goes well with the data described before. Gender ratio of GS was similar in both case series.

There was no difference in the location of GS as reported in other series [1]. We found GS most commonly in the temporo-parietal region, followed by the frontal and parietal. One case of GS was found in the cerebellar region which is an unusual site for GS. In this particular case, GS was seen in a large area within the cerebellum.

Kleihues P, Cavenee in 2000 [1] while giving WHO classification of tumors, described pathology and genetics of tumors of nervous system. GBM may arise more frequently, de novo, after a short clinical history and is called primary Glioblastoma (p53 negative).

Tumors arising from transformation of preexisting astrocytoma are secondary Glioblastomas and this is found to be related with p53 mutation. We found only 3 cases of GS positive for p53, 10 cases were negative. Thus, it appear that majority of our cases are likely to be arising from primary GBM .Similar observation has also been reported in the series of Reis *et al* [20]. They also found p53 mutation in only 26 % of their cases of GBM.

Histopathological examination of the GS shows a biphasic pattern, composed of two components, namely glial and sarcomatous. Sarcomatous component in most cases is fibrosarcoma.

In the present study too, all the 13 cases showed a biphasic pattern. Glial portions were morphologically GBM in all 13 cases. They were highly cellular in most of the cases and all of the cases were having cellular pleomorphism of moderate to high grade.

Sarcomatous portion was showing spindle shaped cell. In most of cases spindle cells were in close proximity to the wall of blood vessels as well as away from the vessel wall. Microvascular proliferation was seen in moderate to higher degree in most of the cases, often with prominent endothelial cell proliferation.

The cell of origin of sarcomatous component has not been fully established.

Feigin and Gross in 1955 suggested that the sarcomatous component in GS develop as a result of neoplastic transformation in markedly hyperplastic blood vessels, commonly found in GBM. Sarcomatous change has been considered to be from endothelial, pericytic or undifferentiated mesenchymal cells. This view has been generally accepted and progressive transformation of sarcoma from hyperplastic blood vessels has been recorded in human as well as in experimental study, reported by Green and Harvey (1968) [11].

Endothelial markers such as factor VIII-related antigen and *Ulex europaeus* agglutinin (UEA-1) have been identified in the sarcomatous tumor cells. However, some studies in recent years have suggested that the sarcomatous component is the result of progressive loss of GFAP in some parts of glioma along with the acquisition of sarcomatous phenotype.

These studies are indicative of origin of both the component from glial cells, the sarcomatous change representing a phenotypic transformation of glioblastoma cells. This change results in negative immunohistochemical staining of such transformed cells for GFAP and they acquire antigenic characteristic of different other cell types. They then react with appropriate antibody such as anti-smooth muscle and anti-desmin antibodies.

Accordingly it is likely that in GS both the components are of monoclonal origin from astrocytes [15].

To evaluate the origin of these spindle cells in sarcomatous areas in the present study GFAP, Reticulin, ASMA and Factor VIII were done. Sarcomatous portion of the tumor was carefully evaluated.

Analysis of reticulin in detail showed that the spindle cells in perivascular areas were in continuum with the vessel wall, suggesting their origin from the wall of the blood vessels in all the 13 cases. Positive cells were flowing out of the wall and forming a complex network around these vessels as well as extending farther away from them. Such a pattern has been described in many cases of gliosarcomas earlier also. This very well support the suggestion of Feigin and Gross [26], that sarcoma in glioblastoma arose secondarily by neoplastic transformation of the cells in hyperplastic blood vessels in response to the presence of a different neoplasm, that is one neoplasm induce the formation of another, unrelated neoplasm.

Factor VIII related antigen is a specific marker of the endothelial cell. We observed Factor VIII positivity, not only in the endothelial cells of vascular lumina but also in the surrounding spindle shaped cells. This supports the hypothesis of vascular origin of sarcomatous component, a "continuum" from the former to the latter. Some earlier studies have described the presence of cells positive for endothelial cell markers in the sarcomatous tumor cells (Schiffer *et al.*,) [12].

ASMA was positive in 8 of our cases. In 2 of them the reaction was strongly positive involving many cells, while in the other 6, it was mild to moderate. Smooth muscular differentiation in GS was described by Haddad et al. Since then a few more cases have been reported (Jones *et al*). In 2 of our cases, the ASMA positive cells appeared to be in continuity with the vessel wall, present in the tumor. Thus it appear that sarcomatous element in GS in some cases arise from the smooth muscle of vessel wall. Haddad et al considered the possibility that malignant glia induce smooth muscle proliferation. This theory fits in well with the observation in our case also. Rarely rhabdomyosarcomatous differentiation has also been reported (Sarkar *et al*) [27].

Variable degree of positivity of GFAP was found in the all the 13 cases, mostly in the areas with GBM. In the sarcomatous areas the GFAP positive cells were absent or were few. Few of the cases showed that in between the mild to high positive areas there were GFAP positive cells intermingling with GFAP negative spindle shaped cells. This goes with the theory of Schiffer *et al*, that variable staining pattern may be related with the degree of anaplasia and it can be regarded as an expression of phenotypic modulation and development of cell population with different genetic properties.

One of our cases of GS showed areas of mucoid diffrentiation. We couldn't see any epithelial differentiation on H&E but GFAP, Factor VIII R/Ag and p53 were strongly positive in this tumor whereas reticulin stain was showing positivity in a focal area. This could be a metaplasia as suggested by Kepes et al in 1982. Metaplastic formation of cartilage has also been described by Kepes *et al* [28].

On the basis of observations made in the present study, there is strong evidence that the sarcomatous component in gliosarcoma arises from the vassel wall. Kochi *et al* [29] suggested a role of histiocytic cells in the development of sarcomatous element in gliosarcoma. They demonstrated monohistiocytic markers in many sarcomatous cells.

In their study, Biernat *et al* reported an identical alteration of the p53 gene in both the components in gliosarcoma. In an in-situ hybridization study, identical alteration in chromosome 10 & 17 has been observed in both the glial and mesenchymal components of gliosarcoma.

The possibility that the sarcomatous component arises from phenotypic change of glioblastoma cells has also been suggested in a study, recently reported by Reis *et al*.

However, from the observation made in the present study and observations made by others, it appear that sarcomatous component in gliosarcoma may have a different cell of origin in different tumor, and we strongly feel that, sarcomatous element do arise, at least in some cases, from the vessel wall, as originally suggested by Feigin *et al*.

SUMMARY AND CONCLUSIONS:

1. All the cases of GBM, showed the age and sex distribution common in fifth and sixth decades and in males with a ratio of 2.38:1.

2. Site of occurence was in cerebrum with involvement of frontal, temporal and parietal lobe in decreasing order of frequency.

3. The common presenting clinical pictures in GBM in our series were headache, mental change and vomiting.

4. The 115 cases of GBM showed generally a variable pattern of cellularity, pleomorphism and necrosis.

5. Microvascular proliferation was seen in all of them in variable amount, including the formation of glomeruloid and other pattern.

6. Some of the cases were showing gemistiocytic cell population of variable amount.

7. Out of these 115 cases, 13 were GS, proven with reticulin, an incidence of 11.3% in our case series, larger than the reported series.

8. The incidence of age and sex distribution of GS was found to be more common in males in age group of 51 to 70 years.

9. The common site affected in GS was cerebrum. There was one case in cerebellum, which is a rare site for GS.

10. Based on the result of staining for p53, primary GS were found to be more common than secondary ones. Stain for p53 being positive in only 3 cases.

11. Analysis of reticulin stain showed positively stained fibers, flowing out of vessel wall in some of the cases, supporting the vascular origin of GS.

12. Factor VIII positivity was seen not only in the endothelial cells of blood vessel but also in the surrounding spindle cells in some cases. This supports the vascular origin of the sarcomatous component.

13. Out of 13 cases of gliosarcoma 8 were positive for ASMA indicating that sarcomatous component was in the form of smooth muscle in these cases and that origin of the sarcoma may be from the smooth muscle of the vessel wall.

14. One of our cases showed mucoid differentiation which can be due to metaplasia.

15. We stongly feel, on the basis of the present study, that the origin of sarcomatous element in gliosarcoma is, at least in some cases, from the vessel wall.

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How to cite this article:
Khanna M, Mendiratta P and Roy S: Clinicopathological study of 115 cases of Glioblastoma multiforme with special reference to Gliosarcoma – An original research article. *Int J Pharm Sci Res* 2013; 4(6); 2384-2392. doi: 10.13040/IJPSR.0975-8232.4(6).2384-92