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Research Article

Study of intraoperative squash cytology of intracranial and spinal cord tumors

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ABSTRACT

Background: The aim was to study the cytomorphology of neoplastic lesions of brain and spinal cord by intraoperative squash cytology, compare it with the histopathological diagnosis on excision biopsy/surgical specimen and establish a correlation. The causes of erroneous diagnoses achieved at squash cytology of intracranial and spinal cord tumors were ascertained. Tumor types having the advantage of diagnostic certainty by squash cytology of intracranial and spinal cord lesions was also determined.
Methods: Squash preparations of 70 patients suspected to have neoplasia were made and stained with rapid hematoxylin and eosin stain and rapid Papanicolaou stain. A few squash smears were also dry fixed and stained with Giemsa stain. The smears were typed according to the cytomorphological criteria and the cytodiagnoses was compared with the histopathological diagnoses and a correlation was established.
Results: A positive predictive value for intraoperative squash cytology for diagnosis of intracranial and spinal cord tumors was seen to be 100% and a negative predictive value of 97.22% were established by this study. The sensitivity was found to be 97.22% and the specificity was 100%. Thus, the accuracy of the study was 98.57%.
Conclusions: Squash smear cytology of the brain and spinal cord tumors performed intraoperatively for diagnostic consultation fulfills all the determinants of an excellent diagnostic modality.

Keywords: Squash cytology, Intracranial tumors, Spinal cord tumors

INTRODUCTION

Pre-surgical diagnoses of a lesion achieved by cytologic methods or by tissue biopsy helps a surgeon plan his surgery and alternative treatments. The diagnosis of intracranial tumors before surgery remained elusive for decades and was achieved only after its grossing and processing in surgical pathology laboratories.[1] Advents in radio-imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) has helped the neurosurgeons but the precision of diagnosis frequently remains debatable.[2] The stereotactic brain biopsy requires technical paraphernalia, technical expertise and operation theatre facilities and thus could not be made available to all operating neurosurgeons.[3] The reliability of frozen section examination of the tissue as an intraoperative diagnostic technique has been questioned due to the inherent artifacts, interpretation and instrumentation involved.[4,5]

The alternative diagnostic modality is small tissue squash cytology/crush smear cytology of CNS lesions obtained intra-operatively. This technique is dependable because of life-like preservation of the cell morphology, minimal technicality involved and rapidity by which a diagnosis

can be achieved and conveyed to the neurosurgeon. It has now been accepted as a standard diagnostic procedure.[6, 7]

In the present study, the cytomorphology of neoplastic lesions of brain and spinal cord by intraoperative squash cytology was studied and compared with the histopathological diagnosis on excision biopsy/surgical specimen and a correlation was established. The causes of erroneous diagnoses achieved at squash cytology of intracranial and spinal cord tumors were ascertained. Tumor types having the advantage of diagnostic certainty by squash cytology of intracranial and spinal cord lesions was also determined.

METHODS

This is a prospective observational study conducted in the Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences from August 2011 to July 2013.

Seventy indoor patients of neurosurgery with space occupying lesions suggestive of neoplasia posted for open biopsy for assessment of surgical management were included in the study. Cases with insufficient tissue quantity not suitable for squash preparation and tissue from stereotactic biopsies were excluded from the study. A proforma with preliminary data of name, age, sex, address, hospital registration number and clinical diagnosis was recorded. The findings of computed tomography (CT) and/or magnetic resonance imaging (MRI) evaluation of the intracranial and spinal cord lesions were recorded for their size, location, number and radiologic diagnoses.

The squash preparations were performed in the operation theatre on a small unfixed piece of tumor tissue, measuring 0.5 to 2mm3 in size, received on saline soaked gauze immediately after removal.[6] Squash smears were made by placing another clean glass slide over it and a gentle pressure was applied as the slides were pulled apart to make the smears of uniform thickness. They were immediately put in 95% ethyl alcohol for 2 minutes for wet fixation and were subsequently stained in the Operation Theatre Complex with rapid hematoxylin and eosin stain and rapid Papanicolaou stain.[7] A few squash smears was also dry fixed to be stained later by Giemsa stain. The squash smears were assessed for their cellularity and were typed according to the cytomorphological criteria described in the literature.[32] The histomorphology of the intracranial and spinal cord lesions were reported based on the criteria described in the standard text.[42,43,44] The intraoperative cytodiagnoses of intracranial and spinal cord tumors were correlated with the final histopathologic diagnoses, the latter being considered as the gold standard. The values of correlation were expressed in terms of sensitivity, specificity, false positives, false negatives, positive predictive value and negative predictive value. The reasoning for false positive and false negative cases was also attempted.

RESULTS

The study comprised of 70 patients. The M: F ratio was seen to be 1:1. Maximum numbers of cases were in the age group of 41-50 years and minimum in 21-30 years. The youngest patient was 1 year old and the oldest was 70 years old.

Table 1: Age and sex wise distribution.

Age group (years)	Total no. of patients (%)	Males	Females
0-10	6 (8.54%)	4	2
11-20	7 (10%)	6	1
21-30	5 (7.14%)	1	4
31-40	14 (20%)	6	8
41-50	16 (22.85%)	8	8
51-60	15 (21.42%)	7	8
61-70	7 (10%)	3	4
Total	70	35 (50%)	35 (50%)

Table 2: Distribution of age with type of lesion.

Age Group (years)	Total no. of cases	Inflammatory lesions	Neoplastic lesions
0-10	6	1	5
11-20	7	1	6
21-30	5	0	5
31-40	14	0	14
41-50	16	2	14
51-60	15	0	15
61-70	7	1	6
Total	70	5 (7.14%)	65(92.86%)

Table 3: Distribution of cytodiagnoses.

Cytodiagnoses		No. of cases (%)	
Tuberculoma		4 (5.17%)	
Neurocysticercosis		1 (1.42%)	
Reactive gliosis		2 (2.85%)	
Meningioma		16 (22.85%)	
Schwannoma		10 (14.28%)	
Pituitary adenoma		2 (2.85%)	
Malignant meningioma		1(1.42%)	
Astrocytoma (All grades)		19 (27.14%)	
Oligodendroglioma		3 (4.28%)	
Medulloblastoma		4 (5.17%)	
Ependymoma		2 (2.85%)	
Metastatic tumors	Embryonal carcinoma	1(1.42%)	(8.57%)
	Squamous cell carcinoma	2(2.85%)	
	Adenocarcinoma	1(1.42%)	
	Ductal carcinoma	1(1.42%)	
	Myeloma	1(1.42%)	
TOTAL		70	

No specific trend of occurrence of malignancy was noted as the intracranial and spinal cord malignant lesions were distributed throughout all age ranges. There were 5 inflammatory lesions (7.14%) and 65 neoplastic lesions (92.86%). The maximum cases of malignancy were noted in age range of 31-60 years (Table 2).

The distribution of the tumors as evaluated by computed tomography (CT) and magnetic resonance imaging (MRI) was – 65 intracranial tumors and 5 spinal cord tumors. Most common cytodiagnoses offered intraoperatively were astrocytoma along with its variants (19cases, 27.14%), meningioma (16cases, 22.85%) and schwannoma (10cases, 14.28%). However, the cytodiagnoses were widely distributed over entities as rare as that of the myeloma (Table 3).

Of the nineteen cases, sixteen cases were cytodiagnosed as astrocytomas (Grade I to III) and 3 cases as glioblastoma multiforme (Grade IV) on squash smears (Table 4). Tuberculoma, neurocysticerosis, meningioma, schwannoma, pituitary adenoma, malignant meningioma, astrocytoma, oligodendroglioma, medulloblastoma, ependymoma and metastatic tumors cytodiagnosed on squash smears had an accuracy rate of 100%. However the process of inflammation was highly suggestive on histological sections. In a group of reactive gliosis, the rate of accuracy was 50%. One case was confirmed to be oligodendroglioma on histopathology. As cited earlier, this was a case of a non-representative tissue sampling for squash preparation. Overall accuracy of squash smear preparations was found to be 98.57% (Table 6).

Intraoperative squash smear cytology in comparison with the final histopathological diagnosis showed no false positive cases. There was one false negative case. This was attributed to non-representative sampling of the tumor tissue for squash preparation. The sensitivity of the squash smear cytology at intraoperative diagnosis was 97.22% while specificity was 100%. The positive predictive value of squash preparation cytology in the diagnosis of CNS and spinal cord tumor was 100% while negative predictive value was 97.22%. The accuracy rate of intraoperative squash cytology for intracranial and spinal cord tumors was 98.57% (Table 7).

Table 4: Cytological grading of Astrocytoma.

Grades of Astrocytoma	Cytology	Histopathology	Discordant Grade on Histopathology	Corrected grade on histopathology (Number)	Concordance with Grade
Grade I	3	3	0	-	100%
Grade II	8	5	3	Grade III- (3)	62.5%
Grade III	5	3	2	GBM-(1)	60%
				Variant* -(1)	
Grade IV (GBM)	3	3	0	-	100%
Total	19	14	5	5	73.68%

*- One case of pleomorphic xanthoastrocytoma

Table 5: Histopathological diagnoses.

Histodiagnoses		No. of cases (%)	
Tuberculoma		4 (5.17%)	
Neurocysticercosis		1 (1.42%)	
Reactive gliosis		1 (1.42%)	
Meningioma		16 (22.85%)	
Schwannoma		10 (14.28%)	
Pituitary adenoma		2 (2.85%)	
Malignant meningioma		1 (1.42%)	
Astrocytoma (All grades)		19 (27.14%)	
Oligodendroglioma		4 (5.17%)	
Medulloblastoma		4 (5.17%)	
Ependymoma		2 (2.85%)	
Metastatic tumors	Embryonal carcinoma	1 (1.42%)	(8.57%)
	Squamous cell carcinoma	2 (2.85%)	
	Adenocarcinoma	1 (1.42%)	
	Ductal carcinoma	1 (1.42%)	
	Myeloma	1 (1.42%)	
TOTAL		70	

Table 6: Comparison of cytodiagnoses with final histopathological diagnoses.

Diagnoses	Number of cases on cytology	Number of cases on histopathology	FN	FP	Accuracy rate (%)	Corrected final diagnosis
Tuberculoma	4	4	-	-	100%	-
Neurocysticercosis	1	1 (chronic encephalitis)	-	-	100%	-
Reactive gliosis	2	1	1	-	50%	Oligodendroglioma
Meningioma	16	16	-	-	100%	-
Schwannoma	10	10	-	-	100%	-
Pituitary adenoma	2	2	-	-	100%	-
Malignant meningioma	1	1	-	-	100%	-
Astrocytoma	19	19	-	-	100%	-
Oligodendroglioma	3	3 + (1*)	-	-	100%	-
Medulloblastoma	4	4	-	-	100%	-
Ependymoma	2	2	-	-	100%	-
Metastatic lesions	6	6	-	-	100%	-
TOTAL	70	70	1	-	98.57%	-

*- the case is added from the category of reactive gliosis as a false negative case

Table 7: Values of correlation of squash smear cytology.

FP	FN	PPV	NPV	Sensitivity	Specificity	Accuracy
0	1	100%	97.22%	97.22%	100%	98.57%

DISCUSSION

The studies reviewed for the present work have observed that there exists no bar for age for the occurrence of the tumors of the CNS.[7,8] The present study too has observed that brain and spinal tumors were distributed in all age ranges similar to the above studies. Studies of Savargaokar, Farmer[7], Kumar et al.[11] and Nigam et al.[34] have reported male predominance in brain tumors. The present study however observed male to female ratio of 1:1 which is contrary to the findings of the above authors and in concordance with studies reported by Torres et al.[8] and Sharma et al.[33]

Many studies on space occupying lesions diagnosed at intraoperative squash cytology reported predominantly the neoplastic pathology over inflammatory pathologies.[1,3,4,5,6,7,8,11,29,31,33,34] The present study has a similar observation regarding distribution of the lesions of neoplastic pathology (92.85%) versus inflammatory pathology (7.14%). The distribution of cytodiagnoses quoted in the major studies of Firlik et al.[3], Cahill, Hidvegi[4], Rao et al.[5], Shah et al.[6], Kumar[11], Torres, Collaco[8], Kini et al.[29], Sharma, Deb[32], Nigam et al.[34], Jha et al.[36] encompasses the inflammatory, benign and malignant neoplastic lesions at intraoperative squash cytology of brain and spinal cord tumors. The variability of intraoperative squash smear cytodiagnoses offered in this study is similar to the above studies. These studies reported astrocytoma as the most common cytodiagnosis which is similar to the findings in the present study.

The commonest cytomorphological features in the squash smears of tuberculoma reported by Asha et al.[1] is presence of lymphocytes, caseous necrosis and fibrotic tissue. The present study apart from these features, also observed groups of distinct epitheloid cells. The corresponding paraffin sections also showed the presence of granuloma on the periphery of the lesion. Asha et al.[1] encountered the difficulty in differentiating the giant cells of glioblastoma multiforme from Langhans giant cells. Present study disagrees with the morphological similarity between the two giant cells as the former carries definite malignant nuclei.

Asha et al.[1] and Cahill, Hidgevi4 reported the cytomorphology of reactive gliosis when astrocytes lacked nuclear atypism. Sharma, Deb[32] reported the morphology of reactive gliosis with well-spaced cells amongst fibrillary material. Findings described in both the above mentioned studies were similar to a case of reactive gliosis diagnosed in the present study. However, a case cytodiagnosed as reactive gliosis was later confirmed on histopathology as an oligodendroglioma.

When cells containing pale cytoplasm with spindle to ovoid, bland nuclei with vesiculation arranged in whorls were seen on squash smears, a cytodiagnosis of meningioma was made by Asha et al.[1], Hinton et al.[12], Salinero et al.[21], Kini et al.[29] and Sharma, Deb.[32] Kini et al.[29] has also reported intranuclear inclusions as a common finding associated with cytomorphology of meningioma. However, in the present study, none of the 16 cases revealed presence of intranuclear inclusions. As

has been cited by Asha et al.[1], the absence of necrosis is one of the highlights of the cytomorphology of meningioma. The present study agrees with the study is in concordance with the above study.

Asha et al.[1], Torres, Collaco8 and Kini et al.[29], reported in the squash smears of schwannoma, a common cytomorphological feature of cohesive, plump, spindle-nuclear cells forming nuclear palisades appearing like verocay bodies. This finding was consistent in the present study. In squash smears of two cases, there was nuclear atypism with enlarged pleomorphic nuclei which was attributed as an ancient change in schwannoma. This cytomorphological feature has not been cited in the literature reviewed. This is a potential feature of error being misinterpreted as a malignant cytomorphology change.

Asha et al.[1], Cahill et al.[4], Inagawa et al.[23] and Kini et al.[29] reported polygonal cells with eosinophilic cytoplasmic granules with sharp, defined margins moderately enlarged nuclei with nucleoli and lack of glial background as a feature of pituitary adenoma and this is in agreement with the observations of the present study.

Many studies have reported grade-I astrocytoma on squash cytology in low to moderately cellular smears with tumor cells showing fine, slender and short projections, increased chromasia and delicate fine chromatin.[1,3,20,29,34] The present study observed cytomorphological features similar to those described by the above authors.

The common cytomorphological features for grade-II astrocytoma were moderate or increased cellularity on smears, unevenly distributed cells, mild nuclear pleomorphism, and increased hyperchromasia without prominent nucleoli, 1-2 layered blood vessels and enlargement of endothelial cells amongst the groups of proliferating astrocytes.[4,22,34] The present study is similar to the above mentioned observations of grade-II astrocytoma.

Diagnostic cytomorphological features for grade-III astrocytoma (anaplastic astrocytoma) on squash smears were moderate to high cellularity, cells with thick cytoplasmic processes, irregularity of nuclei and coarse chromatin in the background of hemorrhagic material. The blood vessel density was increased to 2-3 layers.[1,3,20,28] The present study made a similar observation.

Grade IV astrocytoma had high cellularity of the smears, cells with short and blunt cytoplasmic processes and nuclei showing marked pleomorphism with distinct nucleoli. Nuclei possess coarse, rough chromatin along with presence of mitosis. These smears were also seen to have marked endothelial proliferation and vascular density and glomeruloid structures of endothelial cells. Another prominent feature reported by the studies was multinucleated giant cells and background necrosis.[1,3,13,20,28,33] The present study is in agreement with the features in the squash smears of glioblastoma multiforme.

The cytomorphological features of oligodendroglioma on squash smears were discohesive sheets of small to moderate size tumor cells with round uniform nuclei with inconspicuous nucleoli. The cytoplasm was scant, wispy and discrete with perinuclear-halo. The smears had a few endothelial cells distributed amongst the tumor cells with absence of glial fibres[1,17,19,23,28,31] These features were consistent in the squash smears of oligodendroglioma in the present study. Sharma, Deb38 contradicted that the cells of oligodendroglioma lack the 'fried-egg' appearance on squash smears. The present study reported 'fried-egg' appearance because the smears were fixed in alcohol.

Many studies reported evenly placed uniform cellular smears made up of small round hyperchromatic nuclei with scant cytoplasm, at some places forming Homer-Wright rosettes as a consistent cytomorphological feature for medulloblastma.[1,15,27,23] The present study is in concordance with these studies.

Asha et al.[1], Torres, Collaco[8], Kumar[11] and Kini et al.[29] reported the common features of ependymoma on squash smears with cells unevenly spread in loose sheets perivascularly and in radiating papillary arrangement with uniform, hyperchromatic nuclei of the cells. The present study concords with these observations. Kumar[11] has reported the presence of nuclear groves and intra-nuclear inclusions as a cytomorphologic features which was not observed in the present study.

None of the studies reviewed for the present work have reported the cytomorphology of embryonal carcinoma on squash smears. Firlik et al.[3], Savargaokar, Farmer[7], Torres, Collaco[8], Sharma, Deb[32] and Jha et al.[36] reported germ cell tumor as metastasis but have not described its cytomorphology. The present study reported embryonal carcinoma on squash cytology as the cells did not match the parent cells of the spinal cord tissue and presence of peculiar large cells attempting to form glands was a clue to label it as metastasis.

Cahill et al.[4], Savargaokar, Farmer[7], Torres, Collaco[8], Monabati et al.[14] and Goh et al.[19] quoted that cytodiagnosis of metastasis on squash smears should be made cautiously, the commonest error of glioblastoma multiforme being labeled as metastatic carcinoma.[7] The present study did not encounter any mislabeling. These studies also pointed that the cytomorphology of most metastases are akin for the cytomorphology of their primary malignant tumor.

Reporting of squamous cell carcinoma on squash smear preparations has been quoted by Hernandez et al.[22], Sharma et al.[33] and Jha et al.[36], but none of the studies

have reported its cytomorphology and differences from craniopharyngioma. This may be due to a characteristic recognizable malignant squamous cell cytomorphology being present even at metastasis. The present study has cytodiagnosed 2 cases of squamous cell carcinoma intraoperatively.

The present study encountered a case of a multiple myeloma invading the brain which was cytodiagnosed by the presence of plasma cells, immature plasma cells, plasma cells with varying degree of maturation and plasmablasts in the smears. The same has been mentioned in the study done by Sharma, Deb.[32]

Grading of astrocytoma's on squash smear cytology using the WHO grading has been reported by Cahill, Hidvegi[4], Nassir, Haque[20], Inagawa et al.[28] and Mitra et al.[31] A few encountered the problem of a low grade astrocytoma confirmed on histopathology being reported as a high grade astrocytoma on squash cytology and vice versa. [3,20,23,36] Grading of astrocytomas was the gray zone between reactive gliosis and low grade glioma.[1,7,20] The present study also encountered a similar problem in grading of a few cases as mentioned by the above authors though there were no major fallacies in grading as down grading was not done in any of the 19 cases on histopathological assessment. A study of Sharma et al.[33] adversely commented on grading of astrocytoma on squash smears and imprint cytology. However, the present study disagrees with non-performance of grading on squash cytology as total of 73.68% of grades were in agreement with the final grade on histopathology. Most of the studies attributed to the incompatible grades achieved on histopathology were due to non-representative tissue sampling for squash cytology.

Correlation of cytodiagnoses with histopathology:

The following studies showed 100% correlation of cytodiagnoses with histopathology and are in concordance with the present study:

Abscess and infections[3]

Menigioma [6,8,29,32,34]
Schwannoma [29,32,34]
Pituitary adenoma [29,31,32,34]
Astrocytomas [3,7,20,23,32,34,38]
Oligodendroglioma [6,7,16,31]
Medulloblastoma [6,8,29,31,34]
Epedymoma [6,29,32,34]
Metastasis [6,29,32,34]

Savargaokar, Farmer[7] did not find squash cytology correlative in 7 cases of reactive gliosis. The present study is in partial agreement with the above studies of utility of squash smears for diagnosis of reactive gliosis, as one of the two cases on histopathology was reported as oligodendroglioma. The study of Shah et al.[13] missed a case of malignant meningioma due to inadequate cellularity of the smears. Savargaonkar, Farmer[10] reported one case of malignant meningioma misdiagnosed as a benign meningioma on intraoperative consultation. The present study has cytodiagnosed a case of malignant meningioma on squash smears which correlated with that of the diagnosis on histopathology.

Erroneous diagnoses

Cahill, Hidvegi[3] reported 3 discrepant diagnoses in 32 cases. In the study of Shah et al.[6,16] out of 156 cases had a discrepancy either due to inconclusive material on the smears or with the typing of the tumor. Savargaonkar, Farmer[7] reported 6 discrepant cytodiagnoses which did not affect the benign or malignant disease process but was limited to the type of lesion. Torres, Collaco8 in their series of 307 cases had 22 discrepant cytodiagnoses. These errors occurred due to failure to diagnose the histological type of the lesions. Collaco et al.[16] in his 90 cases had discrepant diagnosis in 24 cases of solid brain lesions. Nasir, Haque[20] in their study of 40 cases, reported 2 discrepant cytodiagnoses. Kini et al.[29] in their 100 cases had 14 discrepant cytodiagnoses. Mitra et al.[31] had 11 discrepant cytodiagnoses out of their 96 cases. Three of these cases were due to error in the grading of astrocytoma. Sharma, Deb[32] in their study had 6 discrepant cytodiagnosis of the 89 adequate cases. Nigam et al.[34] reported 8 discordant diagnoses out of the total 75 cases, not as false negative or false positive diagnosis, but for the type of lesion. Jha et al.[36] in their study of 34 adequate specimens had reported 2 discrepant cases with error in typing of the lesions.

The present study had one false negative and no false positive cases reported on squash cytology. One discrepant cytodiagnosis of reactive gliosis was confirmed as oligodendroglioma on histopathology. It remained undetected on squash cytology due to the non-representative sampling of the tumor. Except for this, the cytodiagnoses were in accord with the final histopathological diagnosis. Similar observation was made in the studies of Asha et al[1], Savargaonkar, Farmer[7] and Nasir, Haque.[20] The present study is in agreement with the reviewed studies that squash cytology can suggest the disease process with high accuracy.

The study of Firlik et al.[3] has reported positive predictive value of squash cytology as 98% and a low negative predictive value of of 66%. The present study is in agreement with the positive predictive value, its value being 100% and in disagreement with the low negative predictive value, its value being 97.22%.

Sensitivity for intraoperative squash cytology for diagnosis of intracranial and spinal cord tumors in the present study was 97.22%. This is in agreement with the high sensitivity quoted by Firlik et al.[3] (96%) and Sharma et al[33] (90.6%).

The present study had a specificity of 100% which is comparable to the high specificity of 87.5% reported by Sharma et al.[33] but Firlik et al.[3] reported a low specificity of 75%.

Almost all studies reviewed for the present work have reported a high accuracy rate of intraoperative squash smear diagnosis of intracranial and spinal cord tumors as more than 80%.[1,3,4,6-8,29,31-34,36] The present study has an accuracy rate of 98.57% which is in agreement with the above studies.

CONCLUSION

When a representative tumor tissue is submitted, the cytomorphology of cellular arrangements and its characters are well depictive to categories lesions under specific diagnostic categories. The sensitivity, specificity and rate of accuracy for squash cytology are high when compared with final histopathological diagnosis. Thus, the squash smear cytology of the brain and spinal cord tumors performed intraoperatively for diagnostic consultation fulfills all the determinants of an excellent diagnostic modality.

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