

Usefulness of Ki-67 in the histological evaluation of neoplastic lesions of central nervous system

P. Shrestha, I. Shrestha, K. Kurisu

Department of Neurosurgery and Neurology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Correspondence to: Prabin Shrestha, Department of Neurosurgery, Graduate School of Biomedical Sciences, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima city, 734-8551, Hiroshima, JAPAN

e-mail: prabinshrestha@hotmail.com

Abstract: Ki-67 is an intranuclear protein, which is present in the proliferating cells. Since it is expressed in only dividing cells, it is an excellent indicator of tissue proliferation in neoplastic lesions. Immunohistochemistry is used to detect Ki67 in tumor tissues. Here, we present few cases where Ki-67 evaluation was very helpful in making final diagnosis.

Cases- Case no. 1 was a case of intracranial mass lesion whose histological finding was confusing, pituitary tumor or astrocytoma. Ki-67 evaluation along with other factors helped in making diagnosis of pituitary adenoma. Case no. 2 was another case of intracranial mass. Ki-67 evaluation ruled out possibility of benign lesion, melanocytoma, though histologically the lesion was not clearly malignant melanoma. Case no. 3 was a case of peripheral spinal nerve tumor, a schwannoma. Its Ki-67 evaluation confirmed that it was of conventional type not cellular.

Ki-67 is a marker of tissue proliferation and higher the Ki-67 expression, higher is the tumor grade and poorer is the prognosis. It also helps in concluding the diagnosis when the histological picture alone is not conclusive. Thus complete histological evaluation, including Ki-67, is necessary before making final diagnosis.

Key words: immunohistochemistry, Ki-67, MIB-1, CNS tumors

Introduction

Ki-67 is an intranuclear protein, which is present in the proliferating cells. It is present in the cells of all phases of cell cycle namely G1, S, G2 and M phase except G0 phase where the cells are in quiescent or resting stage. Thus, determination of Ki-67 is an excellent factor correlating cellular growth. The antibody used for detecting Ki-67 is widely known as MIB-1. Using MIB-1, Ki-67 can be detected by immunohistochemistry. Before the development of Ki-67 detecting technology, assessment of mitotic figures was used to determine tissue proliferation. Ki-67 has been found to be more sensitive than the old method. Proliferating cell nuclear antigen (PCNA) is another protein, which is also used as a proliferation marker. However, unlike PCNA

which not only has a role in DNA replication, but also DNA repair, Ki-67 is virtually restricted in its role as a proliferation antigen, making it a more specific determinant of growth fraction. Simply stating, higher the Ki-67 expression in a tumor, higher is the tumor grade and so is the possibility of malignancy.

KI-67 evaluation in the assessment of any neoplastic lesion of human body including central nervous system is getting more popular as evidenced by literatures.^{1,2}

We present few neoplastic cases of central nervous system where estimation of Ki67 was very useful in making diagnosis. Immunohistochemistry of all the cases were performed in Hiroshima University Hospital, Hiroshima, Japan using standard protocol of an indirect method,

StreptAvidin Biotin (SAB) method.³ The main objective of this article is to emphasize the usefulness of Ki-67, which is hardly evaluated in the developing countries like Nepal.

Case Reports

Case no. 1

A 34 year-old man was admitted in the hospital with an intracranial mass lesion looking like a pituitary tumor. His pituitary hormonal profile was normal. Craniotomy and excision of tumor was done and tumor sent for histological evaluation. Histological report showed that the tumor had astrocytic like component along with pituitary glandular appearance. Since the histological report was not conclusive, immunostaining was performed for several tumor markers along with Ki-67. Ki-67 labeling index (LI) was found to be <1% (Fig. 1). With the result of Ki-67 along with other markers, the diagnosis of pituitary tumor was confirmed.

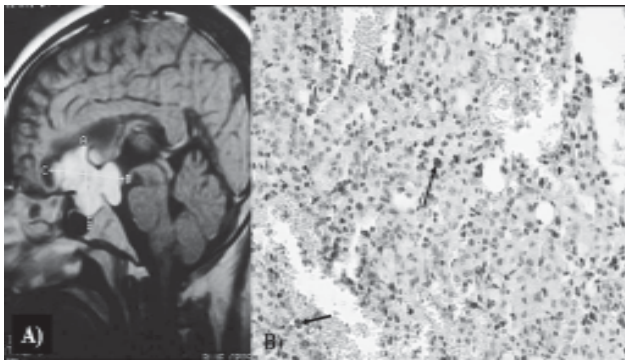


Fig. 1: Case of pituitary adenoma. A) Magnetic Resonance Imaging (MRI), T1W, post gadolinium sagittal section showing well enhanced huge mass lesion in the suprasellar region, B) Ki-67 immunohistochemistry, X 200 magnification, marked by black arrows.

Case no. 2

A 48 year-old man was admitted in the hospital with huge intracranial mass in the right posterior and middle fossa, seemingly originating from leptomeninges. He also had huge congenital cutaneous nevus on the face. Gross total resection of the tumor was done and tissue was sent for histological evaluation. Hematoxylin and Eosin (HE) stain showed few mitosis, cellular atypia and necrosis and histological features of primary leptomeningeal melanoma. Immunostaining was performed for Ki-67 and several other tumor markers. Ki-67LI was >10% (Fig. 2). Though there was no frank signs of malignancy in HE stain, like plenty of mitosis and atypia, possibility of benign lesion was ruled out on the basis of Ki-67 labeling index.

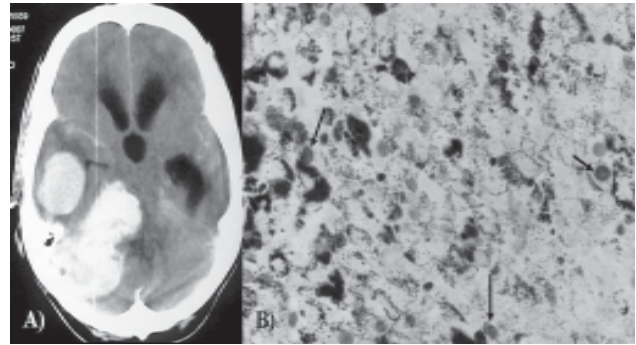


Fig. 2: Case of primary meningeal melanoma. A) Contrast enhanced Computerized Tomography scan showing well enhanced huge mass lesion in right posterior and middle fossa, B) Ki-67 immunohistochemistry, X 400 magnification, marked by black arrows.

Case no. 3

A 35 year-old male patient was admitted in the hospital with a mass lesion in peripheral lumbar spinal nerve. Hemilaminectomy with complete excision was done and tissue was sent for the histological evaluation. HE stain showed highly cellular tumor suggesting schwannoma. Immunostaining for Ki-67 along with other several factors was performed. Ki-67LI was about 2% (Fig. 3). On the basis of Ki67LI, final diagnosis of conventional type, rather than cellular type of schwannoma, was made.

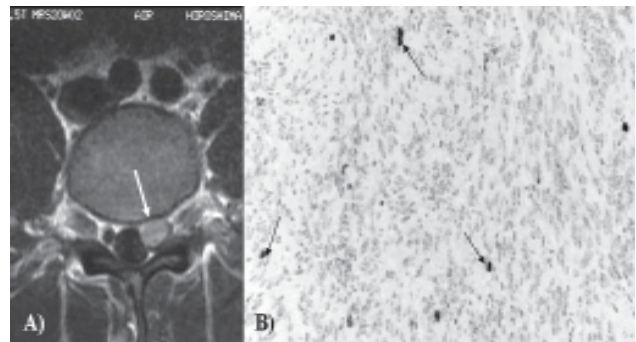


Fig. 3: Case of spinal peripheral nerve schwannoma. A) MRI, T1W, post gadolinium axial section showing well enhanced round mass lesion on the left neural foramen at the level of lumbar 4 vertebra, marked by white arrow, B) Ki-67 immunohistochemistry, X 200 magnification, marked by black arrows.

Discussion

Numerous studies over the last decade have convincingly established the validity of assessing the Ki-67LI as a tumor proliferation indicator. MIB-1 is the monoclonal antibody

developed against the Ki-67 antigen that can be used on routinely fixed paraffin tissue after microwave antigen retrieval. The prognostic value of the MIB-1 labeling index (MLI) or Ki-67LI is great in those tumors where the clinical course is difficult to predict by histologic parameters alone. For example, in breast cancers, Ki-67LI is an independent correlate of both overall survival and disease recurrences,⁴ while in resected non-small cell lung cancers a high Ki-67LI is associated with poor postoperative survival.⁵ Similarly, in ovarian and prostate cancer also expression of Ki-67 proteins offers valuable diagnostic and prognostic information.^{6,7} Irrespective of tumor site or histology, a high Ki-67LI/MLI thus appears to correlate with unfavorable clinical outcome of many human cancers.

Ki-67 does have great value in the histological assessment of neoplastic lesions of central nervous system as well. In the case no.1, Ki-67 had a great value in making final diagnosis though it was not the sole determining factor. Astrocytic tumor usually has Ki-67LI 4-5% if it is benign one and becomes progressively higher as the tumor grade goes up. Anaplastic astrocytoma has Ki-67LI about 5-10% and glioblastoma has up to 15-20%.^{8,2} Pituitary tumors often have low Ki-67LI, usually <1%.^{9,10} Thus, in this case, low Ki-67LI, <1%, along with other factors helped making proper diagnosis. In the case no. 2, histologically, there were few atypia and mitosis. Necrosis was present in little amount. No frank malignant histological picture was present. Thus the lesion could be melanocytoma or malignant melanoma. However, the Ki-67LI was >10%.¹¹ On the basis of this finding, the possibility of benign lesion was ruled out and the diagnosis of intermediate grade melanocytoma or malignant melanoma was made. Similarly, in the case no. 3 also, Ki-67LI was very helpful in making diagnosis. Schwannoma can be conventional or cellular depending on its cellularity and other histological features. Ki-67LI also helps in differentiating between these two. Cellular schwannoma often has Ki-67LI >5%.¹² In our case though the tumor was highly cellular, Ki-67LI was about 2%. Along with other histological findings final diagnosis of conventional schwannoma was made.

With these case illustrations, it is clear that Ki-67 is a very useful tumor marker, which signifies the proliferative activity of a tumor. In advanced countries, histological evaluation is not complete without assessment of Ki-67. However, in developing countries like Nepal, it is still not in common practice yet. Thus complete histological evaluation, including Ki-67, is necessary before making final diagnosis.

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