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Research Article

ASSESSMENT OF PREVALENCE OF MICROSATELLITE INSTABILITY BY IMMUNOHISTOCHEMISTRY IN COLORECTAL CANCER: EXPERIENCE FROM A TERTIARY CANCER CARE CENTRE IN NORTH EAST INDIA

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ABSTRACT

Objective: The aim of our study was to assess the prevalence of Microsatellite instability with the help of Immunohistochemistry in patients presenting with colorectal cancer and correlating MSI status with clinicopathological parameters.
Methods: Retrospective analysis of 61 cases of Colorectal cancer were analyzed who underwent surgery and histopathological examination in our hospital .All clinical information related to patient were retrieved, representative slides were retrieved and revaluation of histological parameters which are predictors of MSI phenotype was done. Representative blocks were selected and Immunohistochemistry for MLH1, MSH2, MSH6 PMS2 antibody were done to assess MSI status
Result: 61 cases of CRC the prevalence of MSI with the help of Immunohistochemistry was found to be 23% (14 cases were MSIH). MSIL was seen in 1.6% (1 case) and MSS in 75.4%(46 cases). MSIH tumours were found to be associated with proximal colon, MSI Histology (Mucinous Carcinoma/Signet ring cell carcinoma/Medullary Carcinoma), TIL Grade III, lymphnode negative status(pN0), low stage(Stage I and Stage II) and statistically significant correlation was found between the above parameters and MSIH.
Conclusion: In our study higher prevalence of MSIH was seen compared to Western literature, stressing the need for more widespread testing for better clinical management and identification of possible hereditary colon cancer syndrome.

INTRODUCTION

Colorectal cancer(CRC) ranks third in terms of incidence but second in terms of mortality worldwide.[1] The incidence of CRC in India is lower than that in the western countries and in India CRC's ranks 13th among all cancer. [2]

In Western countries, most cases of CRC are sporadic, and the hereditary variety accounts for only 10-15% of all cases.CRC mainly develops through a gradual accumulation of genetic and epigenetic alterations of the genome. Molecular changes occurring in colorectal cancer most commonly occurs through chromosomal instability pathway (75%), followed by microsatellite instability (MSI) pathway (15%) followed by CpG island methylator phenotype (CIMP)causing epigenetic gene silencing(10%). [3]

Microsatellites, or Short Tandem Repeats (STRs) are small (1-6 base pairs) repeating stretches of DNA scattered throughout the entire genome and account for approximately 3 % of the human genome. Due to their repeated structure, microsatellites are prone to high mutation rate. MSI is a unique molecular alteration which is the result of a defective DNA mismatch repair (MMR) system.

Testing for MSI is recommended for screening of Lynch syndrome, an autosomal-dominant hereditary disease that is characterized by germline mutations in the MMR genes and associated with an increased risk for several types of cancer including cancers of endometrium, ovary, stomach, small bowel, bladder, kidney, brain, gallbladder, and biliary tract.[4]

Mismatch repair (MMR) gene functionality is tested, either by immunohistochemical (IHC) assessment of protein expression or polymerase chain reaction (PCR)-based assays or by gene sequencing or promoter hypermethylation analysis. The recommended panel in IHC includes markers against protein products of the four MMR genes MLH1 (mutL homolog 1), MSH2 and MSH6 (mutS homologs 2 and 6), PMS2 (postmeiotic segregation increased 2).

MSI-H status is associated with a better prognosis in early-stage CRC and a lack of benefit from adjuvant treatment with 5-fluorouracil in stage II disease. Recently MSI has emerged as a predictor of sensitivity to immunotherapy-based treatments.[5]

In this study the prevalence of MSI in CRC was studied and MSI Status was correlated with clinicopathological parameters.

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MATERIALS AND METHODS

Retrospective analysis of cases of CRC, treated at our hospital over a period of 1 year 4 months was done (January 2019 to March 2021). The study was approved by the Institutional Review Board Ethics Committee.

61 cases of CRC were analyzed who underwent surgery (Hemicolectomy/Transverse colectomy/Segmental ileal resection/ Lower Anterior Resection/ Abdominopelvic resection) and histopathological examination in our hospital
All clinical information related to patient was retrieved from the records of our hospital information system.

Representative slides were retrieved and revaluation of histological parameters which are predictors of MSI phenotype was done. Also the extent of tumor invasion, tumor and nodal stage, margin status, lymphovascular invasion, and perineural invasion was recorded. Stromal TIL was graded at the invasive front. After viewing the H &E sections, cases for IHC were selected. IHC was performed against protein products of the four MMR genes MLH1, MSH2 and MSH6, PMS2. The interpretation of IHC staining was carried out independently by two pathologists. The complete absence of nuclear staining in the presence of positive internal control (lymphocytes and stromal cells) was considered negative (loss of expression). Aberrant staining patterns included cytoplasmic staining or nuclear staining in <10% cells IHC was repeated and if the aberrant staining pattern persisted after repeat IHC, it was considered non-contributory. Cases where internal control did not work even after repeat TMA or whole tumor section staining, were regarded as noncontributory and excluded from the study.IHC was reported as:

1. **MSI – low (MSI-L) -** 1% - 29% of markers exhibit loss of nuclear expression and 1 of the markers exhibit instability
2. **MSI – high (MSI-H)** -≥30% of the markers exhibit loss of nuclear expression and 2 or more of the markers exhibit instability
3. **MSI – stable (MSS)-**intact nuclear expression

Statistical analysis: All data were analyzed using (SPSS Software 22). Association between MSI status and other parameters were evaluated using Chi-square test and Fischer's exact test wherever applicable. A p value <0.05 was considered as statistically significant at 95% Confidence Interval.

RESULTS

Total of 61 patients histopathologically confirmed as colorectal cancers formed the study population

Age: Among 61 cases of CRC mean age of presentation was 51 years with age ranging from 19 to 81 years. Mean age of presentation for MSI H tumours was 46 years and for MSS tumours was 54 years. No statistical correlation was found between MSI status and age of presentation (p value-0.095)

Gender: Our study found male preponderance with male to female ratio of 1.17:1. MSI H tumors also showed a male preponderance. There was no significant correlation found between gender and MSI status.(p value-0.146)

Site of Involvement: The most common site of involvement was found to be ascending colon (29%) followed by rectum and sigmoid colon. In our study proximal colon involvement (60.6%) was more common than distal colon (39.4%).There was statistical correlation found between proximal colon tumours and MSI H status (p value -0.042)

Size: Overall mean size of the tumour was 5.32cm .MSIH was found to have more mean size (6.57cm) than MSS/MSIL (4.94cm). There was no statistical significant correlation between tumour size and MSIH status (p value-0.232)

Stage: Most cases presented at Stage II (62%) followed by Stage III (23%) followed by Stage I (10%) and Stage IV(5%). MSI H tumour presented at earlier stage (Stage I and Stage II). No MSIH tumours were found to have Stage III and Stage IV. There was statistically significant correlation found between MSIH status and stage. (p value-0.04) .

Table 1 Association between clinicopathological parameters and MSI status

	MSS	MSIH	Total	p value
Age				
<40	7(58.3)	5(41.7)	12(100)	0.095
>=40	40(81.6)	9(18.4)	49(100)	
Gender				
Male	23(69.7)	10(30.3)	33(100)	0.146
Female	24(85.7)	4(14.3)	28(100)	
Site				
Distal	22(91.7)	2(8.3)	24(100)	**0.042**
Proximal	25(67.6)	12(32.4)	37(100)	
MSI histology				
MSI histo(Mucinous/SRC/ Medullary)	2(18.2)	9(81.8)	11(100)	**<0.001**
Non MSIH Histo	45(90)	5(10)	50(100)	
TIL Grade				
1	17(100)	0(0)	17(100)	
2	28(100)	0(0)	28(100)	**<0.001**
3	2(12.5)	14(87.5)	16(100)	
Lymphnode Status				
Positive	13(100)	0(0)	13(100)	**0.027**
Negative	34(70.8)	14(29.2)	48(100)	
Tumour Size				
<5cm	22(84.6)	4(15.4)	26(100)	0.232
>=5cm	25(71.4)	10(28.6)	35(100)	
LVI				
Negative	43(76.8)	13(23.2)	56(100)	0.87
Positive	4(80)	1(20)	5(100)	
PNI				
Negative	44(75.9)	14(24.1)	58(100)	0.332
Positive	3(100)	0(0)	3(100)	
Stage				
Stage I	3(50)	3(50)	6(100)	
Stage II	27(71.1)	11(28.9)	38(100)	**0.04**
Stage III	14(100)	0(0)	14(100)	
Stage IV	3(100)	0(0)	3(100)	

Personal and family History of any other cancer

Only 1 case of a 41 year female there was previous history of endometrial cancer 5 years back .This case showed MSIH status in colon. Patient didn't have any family history of cancer.

Histopathology: Most common histological type in our study among all CRC was found to be Well differentiated Adenocarcinoma. In MSIH tumours most common type of histology seen were signet ring cell carcinoma , mucinous carcinoma and medullary carcinoma. Medullary Carcinoma was diagnosed in 1 case which showed MSI H status on IHC. Crohn's like lymphocytic aggregates were seen only in 2 cases of MSIH tumours. MSI H tumours usually show MSIH histology. There was significant correlation found between MSI H and MSIH histology.(p value <0.001)

LVI and PNI status: Among 61 cases LVI was present in only 5 cases out of which 4 cases were MSS.PNI was present in only 3 cases out of which all were MSS. No significant

correlation was found between LVI and PNI status with MSI status.(p value -0.87 and 0.332 respectively)

Adjacent colon: Only 1 case showed tubulovillous adenoma in adjacent colon and another case showed features of hyperplastic polyp but both of these cases were MSS. A 43 year old male showed multiple lesion involving caecum and sigmoid colon. Both the lesions were diagnosed as Well differentiated Adenocarcinoma. This case was found to have MSIH status. To prove its significance more cases are required.

Metastasis at presentation: 5 cases showed metastasis at presentation. Out of which 3 cases had metastasis to liver and liver metastatectomy was done.2 cases showed metastasis to ovary which was confirmed with the help of IHC (CK7 negative and CK20 positive in ovarian lesion suggested Metastasis).

In both the ovarian metastasis cases total abdominal hysterectomy with salpingoophorectomy was done. Peritoneal metastasis was seen in 2cases and both were MSS.

No. of lymphnodes retrieved: Average no. of lymphnode retrieved were 16.7 in MSI H status patients and 12 in MSS status. There was statistically significant correlation found between mean number of lymphnodes retrieved and MSI status.(p value-0.034) Higher yield of lymphnodes are seen in MSI H tumours.

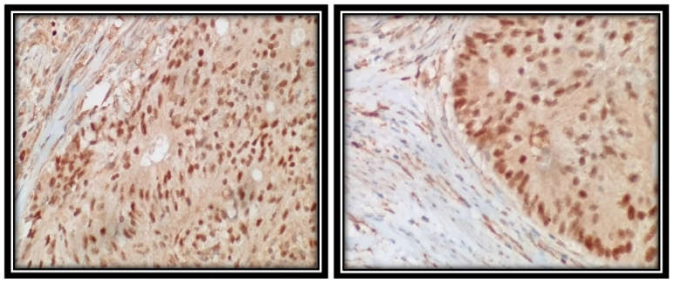

Figure 1 and 2 40x IHC showing nuclear positivity for MLH1 and PMS2 (Dual Intact)

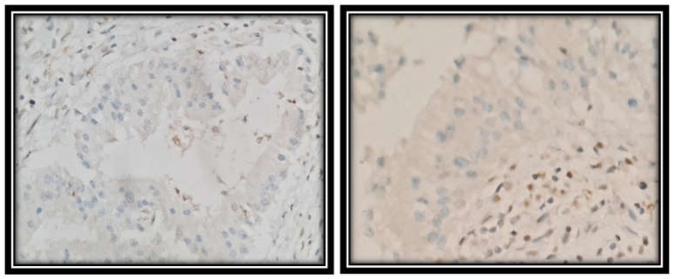

Figure 3 and 4 40x IHC showing nuclear loss of MLH1 and PMS2 (Dual loss). Internal control stromal cells and lymphocytes are positive

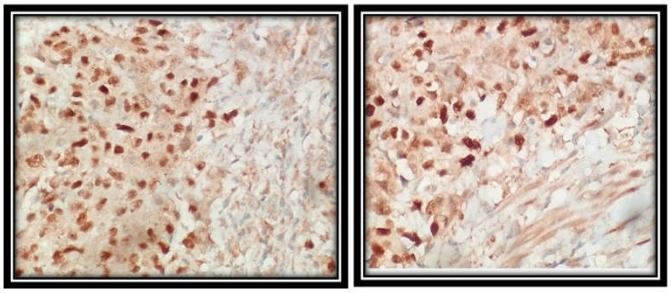

Figure 5 and 6 40x IHC showing nuclear positivity for MSH2 and MSH6 (Dual Intact)

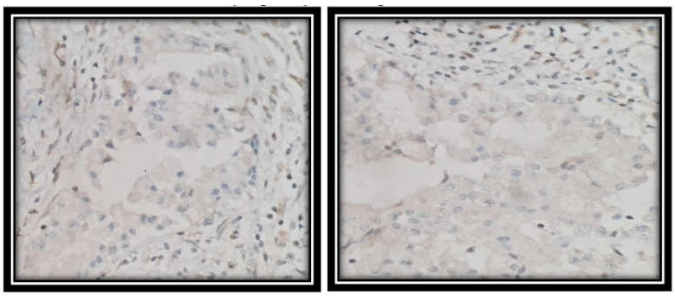

Figure 7 and 8 40x IHC showing nuclear loss of MSH6 and MSH2 (Dual loss). Internal control stromal cells and lymphocytes are positive

Lymphnode status: 21.3% (13cases) showed lymphnode positivity. Statistically significant correlation found between lymphnode status and MSI status (p value-0.027)

TIL status: In our study High grade TIL (TIL Grade III) showed statistically significant correlation with MSI status suggesting MSIH tumours show High grade TIL(Grade III) (pvalue-<0.001).TIL grade III was seen in 87.5% of MSIH tumours.

Immunohistochemistry: Out of 61 cases MSIH was seen in 23 % (14 cases), MSIL in 1.6% (1 case) and MSS in 75.4%(46 cases). Among MSIH cases most commonly MLH1 and PMS2 dual loss was seen followed by dual loss of MSH2 and MSH6. PMS2 loss was seen in only 1case (considered as MSIL) According to the above table MSIH tumours are associated with proximal colon, MSI Histology(Mucinous Carcinoma/ Signet ring cell carcinoma/Medullary Carcinoma),TIL Grade III, lymphnode negative status(pN0), low stage(Stage I and Stage II) and statistical significant correlation was found between the above parameters and MSIH status.

No statistical significant correlation was found between age, gender, tumour size, LVI, PNI status and MSI H status.

DISCUSSION

CRC is more common in Western countries. It ranks 3rd in terms of incidence worldwide while in India it ranks 13th. [1]The difference in incidence is mostly due to lifestyle and dietary habits.

The mean age of diagnosis for CRC in the Western countries is 65 years.[6] Published data from Deo *et al*. and Pal *et al* have shown that CRC occurs in a comparatively younger age group in India with the average age of diagnosis being 20 years earlier than in the West.[7,8] Data from Tata Memorial Hospital has also revealed that the mean age at diagnosis of CRC to be 50 years, again much earlier than the Western patients.[9]

In a study from eastern India on 168 patients with sporadic CRC, the mean age of presentation was 47.01 years, while it was 58.4 years in a retrospective descriptive analysis of 220 cases of CRC.[10,11] In another study from central India, on 233 patients over 8 years, the median age at diagnosis was 43 years with 39% of CRC patients being diagnosed at the age of 40 or younger.[12] Other studies from India though on a small number of patients show similar results which elicits the question whether CRC occurs at a younger age in India .[13] In another study from central India by Hussain *et al*, on 233 patients over 8 years, the median age at diagnosis was 43 years with 39% of CRC patients being diagnosed at the age of 40 or younger .[14] In our study 19.6% of cases presented at <40 years. In another study by Sudarshan *et al* among 233 patient 39.05% presented at a age <40years. [15] In a study by Rai *et al.* MSIH tumours had a mean age of 49 years, while MSS tumours had a mean

age of 50 years. [16] In our study the mean age of presentation was 51 years and the mean age of presentation for MSI H tumours was 46 years and for MSS tumours was 54 years.

In a study by Dubey *et al*., a male preponderance in their study.[17] There is another study by Rai *et al* similar results were found.[16] Overall colorectal cancers have a male predominance

In a study by Maharaj *et al*. showed that rectal cancers amounted to around 64% compared to 36% colonic cancers, a ratio of almost 1.8:1.[18] Deo *et al*. also reported that there was a strong preponderance of rectal cancer over colonic cancer (76% versus 24%).[19] In contrast a study by Rai *et al*. most common location was ascending colon (38%). [16] In our study also most common site was ascending colon (29%) followed by rectum(15%) and sigmoid colon (15%). Left-sided tumors are more likely to present with overt bleeding per rectum and pain and therefore are more likely to become symptomatic earlier. In another study by Parc *et al* right sided colon cancers were associated with MSIH tumours.[20] This was found to be similar to our study.

Colorectal cancer in Lynch syndrome has a propensity to involve the proximal colon with 70% arising proximal to the splenic flexure, the figures of which are opposite to sporadic cancers.[21] Also in our study out of 14 cases of MSIH 12 cases presented in proximal colon(85.7%). In a similar study by Nayak *et al* in 77.4% MSIH tumours involvement of proximal colon was seen.[9]

In a study by Suryadevara *et al* out of 171 cases,69 presented at Stage III (51%) followed by Stage II(28%). [22] In our study most of the cases presented at Stage II(62%) followed by Stage III(23%) followed by Stage I(10%) and Stage IV(5%).In a study by Ogino *et al*. MSI was found to be more common among stage II (~20%) than stage III (~12%) CRC and is even less frequent among stage IV CRC (~4%). [23] In another study by Roth *et al* it was stated that the incidence of MSI decreases with stage of tumor being the highest in Stage II CRC. [24] Comparable results were obtained in our study where out of MSIH tumours 11 cases (78.5%)presented at Stage II.

In a study by Nayak *et al*. MSI H histology (Mucinous, signet ring cell, medullary) was seen in 43.4% of cases of MSIH tumours and 21.3% cases of MSS tumours.[9] In our study 81.8% of MSIH tumours showed MSIH histology.

It is believed that MSI H tumors are more likely to elicit a stronger immune response as they are more antigenic. The higher lymph node yield in these cases may represent reactive lymph node changes rather than invasion by tumor cells. According to few studies low lymphnode yield has been associated with poorer survival outcome in stage II and III colorectal cancer.[25] Tumors with high LN yield (>10) were significantly associated with the MSI phenotype in a study by Belt *et al*. [26] In our study average no. of lymphnode retrieved were 16.7 in MSI H status patients and 12 in MSS status.

In a study by Parc *et al*. it was found that MSI and microsatellite stable (MSS) tumours did not differ in terms of perineural or lymphovascular invasion. [20] In our study there was no significant correlation was found between LVI and PNI status with MSI status.

In a study it was found that MSI-H tumors are also less likely to metastasize to lymph nodes or distant sites, compared to MSS tumors. [27,28] Similarly in our study none of the MSIH tumours showed lymphnode metastasis and significant correlation was found between MSI status and lymphnode status Stromal TILs are likely to be the most important factor for the formation and maturity of the tumor microenvironment. In a study by Fusch's *et al* in 1034 patients International TILs Working Group system (ITWG)for assessing TILs was found to be a powerful predictor of all-cause survival in CRC independent of many prognostic factors and superior to the assessment of intraepithelial lymphocytes using other traditional scoring system. In our study TILs in the stroma at invasive front were identified according to recommendations by the ITWG , 2014 .[29]

According to western literature approximately 15% of all CRCs display MSI. Very few Indian studies have reported the prevalence of MSI in CRC. In a study by Nayak *et al* loss of MMR IHC was seen in 53/231 cases, i.e. 22.94%. [9] In another study by Kanth *et al*. in 91 cases frequency of MSI-H phenotype observed was 48.4%. [30] Slightly higher prevalence of MSI-H phenotype was seen in Indian studies compared to Western literature, stressing the need for more widespread testing for better clinical management and identification of possible hereditary colon cancer syndrome. While in another study by Pandey *et al*. in a series of 46 cases, observed MSI – H was 15.7% which is similar in prevalence to western literature.[31] In our study MSI H was seen in 23% cases.

MSI-H phenotype is characterized by clinical and pathologic features distinct from those observed in MSS CRC, such as age <40 years, poor differentiation and mucinous, medullary, signet ring cell histology, prominent lymphocytic infiltration, right-sided colon location, and early stage at diagnosis. In a study by Nayak *et al* [9] significant independent predictive variables associated with MSI were age <60 years, right‑sided colonic location and the presence of severe Intratumoral lymphocytic infiltration. In our study significant correlation was found between MSI and proximal colonic location, TIL grade 3

MMR gene functionality is tested most commonly either by immunohistochemical (IHC) or polymerase chain reaction (PCR). IHC is preferred because it is inexpensive, widely available in most pathology laboratories. In a study by Cicek *et al* IHC estimation of MMR deficiency has similar efficacy to PCR based MSI with a sensitivity close to 95% and specificity of 98%.[32]

MMR genes including MLH1, MSH2, MSH6, and PMS2 are an important pathway in colorectal carcinogenesis. In a study by Southey *et al*. [33] IHC with MLH1/MSH2 has a lower sensitivity than MSI testing by PCR in predicting gene mutation; however, inclusion of PMS2 and MSH6 significantly increases the sensitivity of IHC, resulting in a predictive value that is virtually equivalent to that of MSI testing by PCR. The majority of CRC with MSI-H has a loss of expression of MLH1 and PMS2 protein. Sporadic CRC with MSI-H include the absence of significant familial clustering, absence of MLH1 and PMS2 proteins, and frequent mutation (usually V600E). [34]

MSI high/MMR deficient tumors have been shown to have a better outcome when compared to MSS/MMR proficient tumours. A meta-analysis of 7642 CRC patients, including 1277 MSI-H patients, showed that MSI-H tumors were associated with a better prognosis than microsatellite stable (MSS) tumors. [35] Our study will also be later assessed for prognosis.

The limitations of the study are as follows: the sample size was small. IHC is just a screening tool for Lynch syndrome ,further sequencing and methylation studies are required to confirm Lynch syndrome. Although IHC is very sensitive and specific for the detection of MSI, it does come with certain drawbacks. The IHC staining pattern may not be uniform throughout the tumor, IHC will be negative for MSH2 staining in the presence of EPCAM deletion, and certain frameshift mutations are associated with truncated protein production with retained antigenicity.[34] Cancers of the colon and the rectum were pooled together although their biological behavior and pathological basis are different. Treatment outcomes were not analyzed and prognosis was not estimated since it was more of a prospective study. This study will be further evaluated for prognosis.

CONCLUSION

To summarize in our study out of 61 cases of CRC the prevalence of MSI with the help of Immunohistochemistry was found to be 23% (14 cases were MSIH). MSIL was seen in 1.6% (1 case) and MSS in 75.4% (46 cases). Among MSIH cases most commonly MLH1 and PMS2 dual loss was seen followed by dual loss of MSH2 and MSH6. PMS2 loss was seen in only 1case which was considered as MSIL.

In our study MSIH tumours were found to be associated with proximal colon, MSI Histology (Mucinous Carcinoma/Signet ring cell carcinoma/Medullary Carcinoma),TIL Grade III, lymphnode negative status(pN0), low stage(Stage I and Stage II) and statistically significant correlation was found between the above parameters and MSIH. No statistical significant correlation was found between age, gender, tumour size, LVI, PNI status and MSI H status. Mean total number of lymphnodes retrieved was also found significantly higher in MSIH tumours.

With the advent of Immunotherapy, MSI testing should be advised for all CRC especially in low stage tumours (Stage I and II). MSI testing is recommended for screening of Lynch syndrome and it provides prognostic information for better patient care. MSI-H status in Stage II tumours also lacks benefit from adjuvant treatment with 5-fluorouracil, hence MSIH testing is of outmost importance in Stage II tumours.
In our study higher prevalence of MSIH was seen compared to Western literature, stressing the need for more widespread testing for better clinical management and identification of possible hereditary colon cancer syndrome.

In spite of the huge therapeutic significance, in India, there is currently not much published series on the prevalence of MSI in CRC. This study was done to evaluate the prevalence of MSI in our institute and will be further evaluated for prognosis.

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