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The Comparison between Clinical and Pathological Features of Testicular Seminomatous and Nonseminomatous Germ Cell Tumors

Didar Gürsoy[1], İlke Evrim Seçinti[1], Fatih Gökalp[2], Sibel Hakverdi[3], Sadık Görür[4]

[1] Asst. Prof., Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Pathology, Hatay, Turkey.
[2] Asst. Prof., Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Urology, Hatay, Turkey.
[3] Prof., Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Pathology, Hatay, Turkey.
[4] Prof., Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Urology, Hatay

Öz

Testiküler Seminomatöz ve Nonseminomatöz Germ Hücreli Tümörlerin Klinik ve Patolojik Özelliklerinin Karşılaştırılması

Amaç: Bu çalışmada merkezimizde son 10 yılda tanı alan testiküler seminomatöz ve non-seminomatöz germ hücreli tümörlerin klinik ve histopatolojik özelliklerinin farklarını araştırmayı amaçladık.
Gereç ve Yöntem: Ocak 2010'dan Mayıs 2020'ye kadar merkezimizde histopatolojik olarak kanıtlanmış testiküler germ hücreli tümör tanısı olan tüm hastalar çalışma kapsamına alındı. Medikal kayıtlar taranarak hastalara ait Hematoksilen-Eozin (H+E) boyalı preparatlar yeniden değerlendirildi. Tümörlerin sınıflandırılmasında ve primer tümörün evresinin belirlenmesinde (pTs) 2016 Dünya Sağlık Örgütü Üriner Sistem ve Erkek Genital Organları Tümörleri Sınıflaması esas alındı.
Bulgular: Çalışmamıza dâhil olan olguların 27 tanesi (%51) SEM, 26 tanesi (%49) ise NSE-GHT morfolojisinde idi. SEM grubunda hastaların yaş aralığı 23-55 yıl (minimum-maksimum) arasında değişmekte olup ortanca yaş 33 yıl (IQR=26.0-41.0 yıl) iken NSE-GHT'ler için bu değerler sırasıyla 16-44 yıl ve 28 yıl (IQR=22.75-29.5 yıl) idi. Alt grup ayrımı yapılmaksızın pTs değerlendirmesine göre 21 tümör (%39.6) Evre 1, 31 tümör (%58.5) Evre 2 ve 1 tümör (%1.9) Evre 3 idi.
Sonuç: Testis kanserleri genç erkeklerde en sık görülen malignite olup son yıllarda insidansı artış göstermiştir. Komplet kür oranı, erken tanı ve bu tümörlerin yüksek düzeyde kemo- ve radyosensitif olmasından dolayı %100'e yakındır.
Anahtar Kelimeler: Testis Kanseri, Germ Hücreli Tümör, Seminom, Non-Seminomatöz Germ Hücreli Tümör

Abstract

The Comparison between Clinical and Pathological Features of Testicular Seminomatous and Nonseminomatous Germ Cell Tumors

Objective: In the present study, it was aimed to investigate the differences between the clinical and histopathological features of testicular seminomatous and non-seminomatous germ cell tumors diagnosed in our center in the recent 10 years.
Methods: All the patients in whom diagnosis of testicular germ cell tumor was histologically confirmed in our center between January 2010 and May 2020 were involved in the study. The medical records of the patients were screened and Hematoxylin-Eosin (H+E) stained slides of the patients were re-evaluated. The tumor classification and primary tumor stage determination (pT) were carried out in accordance with the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs.
Results: The morphology of seminoma (SEM) and non-seminomatous germ cell tumors (NSE-GCTs) were identified in 27 (51%) and 26 (49%) of the study patients, respectively. In the SEM group, patient ages ranged between 23-55 years (min-max) and median age was 33 years (IQR=26.0-41.0) while those values for the NSE-GCT cases were 16-44 years and 28 years (IQR=22.75-29.5), respectively. The evaluation of the pTs without subgroup discrimination demonstrated that 21 (39.6%), 31 (58.5%) and 1 (1.9%) of the tumors were Stage 1, Stage 2 and Stage 3, respectively.
Conclusion: Testicular cancers are the most frequently seen malignancy in the young males and its incidence has increased in the recent years. The complete cure rate is approximately 100% thanks to early diagnosis as well as high chemosensitivity and radiosensitivity of these tumors.
Keywords: Testicular Cancer, Germ Cell Tumor, Seminoma, Non-Seminomatous Germ Cell Tumor

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Sorumlu Yazar/Corresponding Author: Asst. Prof. Didar Gürsoy
Email: gursoydidar@gmail.com
ORCID iD: 0000-0002-0674-7047

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INTRODUCTION

Testicular cancers (TC) constitute 1% of cancers in males worldwide (1, 2). Besides, they represent 5% of urological tumors (3). Testicular cancer is the most common malignancy among young males and its incidence has increased in the recent years (4, 5). It is most frequently identified in the 2nd-4th decades of life (1, 3, 6). Various factors have been blamed etiologically. These factors include undescended testicle, infertility, and the presence of testicular cancer in the first-degree relatives, the presence of tumor in the other side, Klinefelter's Syndrome and testicular microlithiasis. Trauma, infectious causes, occupational and hormonal factors are blamed less frequently for etiology (1, 4, 5).

A great majority of testicular cancers (95%) develop from the germ cells of the testicle (1). Testicular germ cell tumors (TGCT) are divided into two main groups as seminomas (SEM) and non-seminomatous germ cell tumors (NSE-GCT). Yolk sac tumor (YST), embryonal carcinoma (EC), choriocarcinoma (CC), teratoma (TE) and mixed germ cell tumors (MGCT) are the tumors classified under the title of NSE-GCT. Seminomas are the most frequently seen testicular tumors and they make up approximately half of all TCs. Although, spermatocytic tumors are also from the class of germ cell tumors, however, they are different from other germ cell tumors by being unrelated with germ cell neoplasia in situ (7). The first-line treatment of TGCTs is inguinal orchiectomy. The rate of complete cure is approximately 100% (8). The treatment options to be performed following orchiectomy may vary depending on pathological diagnosis, stage and risk factors (2).

In the present study, it was aimed to investigate the differences between clinical and histopathological features of testicular seminomatous and non-seminomatous germ cell tumors diagnosed in our center in the recent 10 years.

MATERIALS AND METHODS

All the patients in whom diagnosis of testicular germ cell tumor was histologically confirmed in our center between January 2010 and May 2020 were involved in the study. The medical records of the patients were screened and data such as age, hospital admission complaints, levels of preoperative (pre-op) tumor marker and type of the performed surgery were obtained. The tumors were grouped as SEM and NSE-GCT (YST, EC, CC, TE, MGCT). Data on laterality, focality and diameter of the tumors were obtained from the pathology reports. The greatest tumor diameter described as tumor size by macroscopic assessment was expressed in terms of millimeter. Hematoxylin-Eosin (H+E) stained slides of the patients were re-evaluated by two pathologists (DG, IES) to review regarding the presence of intratubular germ cell neoplasia, positivity of spermatic cord surgical margin, the presence of tumor in the soft tissue surrounding spermatic cord, lymphovascular invasion (LVI), rete testis invasion, epididymal invasion, tunica albuginea invasion, and primary tumor stages (pT) of the patients were determined. The tumor classification and primary tumor stage determination (pT) were carried out in accordance with the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs (7).

Statistical Analysis

The data obtained from the study were analyzed using IBM SPSS Statistics 21 software package. Shapiro Wilk test was used to determinate normally distributed. Quantitative variables were expressed as median and Interquartile range (IQR) while categorical variables were expressed as number (n) and percentage (%). Chi-square test or Fisher's exact test were used to compare qualitative data. The difference between SEM and non-SEM groups regarding qualitative data was analyzed by Mann-Whitney U test. A $p<0.05$ value was accepted as statistically significant.

RESULTS

It was analyzed totally 62 TGCT cases in this study. Nine cases that were sampled and undergone their initial pathological evaluation in an external center and sent to our department for consultation, clinical information and some pathological data of these cases could not be reached. These cases were excluded from the study. The morphology of SEM and NSE-GCT were identified in 27 (51%) and 26 (49%) of the patients included in this study, respectively. The analysis of the NSE-GCTs regarding subgroups revealed the morphology of EC and MGCT in 8 (30.8%) and 18 (69.2%) cases, respectively. It was identified no tumor with morphology of pure YST, CC and TE. SEM, EC and MGCT morphologies were shown (Figure1, 2, 3). In the SEM group, patient ages ranged between 23-55 years (min-max) and median age was 33 years (IQR=26.0-41.0) whereas those values for the NSE-GCT cases were 16-44 years and 28 years (IQR=22.75-29.5), respectively. A statistically significant difference was present between the SEM and NSE-GCT groups with respect to age at diagnosis ($p=0.003$).

The review of the hospital admission data without subgroup discrimination showed that 43 (81.1%) and 10 (18.9%) patients applied due to the complaints of palpable mass and palpable painful mass in the testicle, respectively. Pain was present at time of diagnosis in 6 (22.2%) cases in the SEM group whereas 4 (15.4%) cases had pain at time of diagnosis in the NSE-GCT group. The SEM and NSE-GCT groups demonstrated similar rates of hospital admission due to pain ($p=0.728$). The pre-op tumor marker levels of 50 (94.3%) patients could be obtained from the medical records. High levels of LDH, AFP and ß-HCG were detected in 15 (55.6%), 1 (3.7%) and 2 (7.4%) patients in the SEM group, respectively. Totally 4 (14.8%) patients had concurrent high levels of two markers (2 patients with concurrent high levels of ß-HCG and LDH

and 2 patients with concurrent high levels of AFP and LDH) while tumor marker levels were within normal limits in only 3 (11.1%) patients. On the other side, high levels of LDH, AFP and ß-HCG were found in 3 (12%), 1 (4%) and 1 (4%) patients in the NSE-GCT group, respectively, concurrent high levels of two markers were identified in 7 (28%) patients while all the tumor marker levels were higher than normal limits in 8 (32%) patients. Tumor marker levels were within normal limits in 5 (20%) patients. Radical inguinal orchiectomy was performed in majority (96%) of the patients whereas 2 (4%) patients were undergone partial orchiectomy. In the SEM group, tumor diameter ranged between 10-120 (min-max) mm while median value of tumor diameter was 38 mm (IQR=22.0-80.0). Those values in the NSE-GCT group were 15-160 mm (min-max) and 37.7 mm (IQR=23.0-51.25), respectively. No statistically significant difference was determined between the SEM and NSE-GCT groups in terms of tumor size (p=0.631).

Tumors were located at the right and left testicles in 13 (48.1%) and 13 (48.1%) in the SEM group, respectively. On the other side, 17 (65.4%) and 9 (48.1%) of the tumors were located at the right and left testicles in the NSE-GCT group, respectively. Bilateral tumors were present in 1 (2%) case and these tumors showed morphology of seminoma. Two (4%) cases were multifocal in this study. Among all TGCTs, rete testis invasion, epididymal invasion, tunica albuginea invasion, LVI, intratubular germ cell neoplasia component and the presence of tumor in the soft tissue surrounding spermatic cord were encountered in 16 (30.1%), 13 (24.5%), 16 (30.1%), 22 (41.5%), 19 (36%) and 1 (1.9%) of the cases, respectively. It was detected tumor at the spermatic cord surgical margin in none of the cases. The distribution of the histological characteristics in the SEM and NSE-GCT groups was summarized (Table 1). The analysis regarding primary tumor stage revealed that most of the SEM and NSE-GCTs were stage 2 and their rates were 63% and 53.9%, respectively. The evaluation of the pTs without subgroup discrimination demonstrated that 21 (39.6%), 31 (58.5%) and 1 (1.9%) tumors were stage 1, stage 2 and stage 3, respectively. None of the patients had pTis or pT4 tumor. In the SEM group, 10 and 17 tumors were pT1 and pT2 (Chart 1), respectively. In the NSE-GCT group, 11, 14 and 1 tumors were pT1, pT2 and pT3, respectively (Chart 2). No statistically significant difference was determined between the SEM and NSE-GCT groups in terms of primary tumor stage (p=0.836).

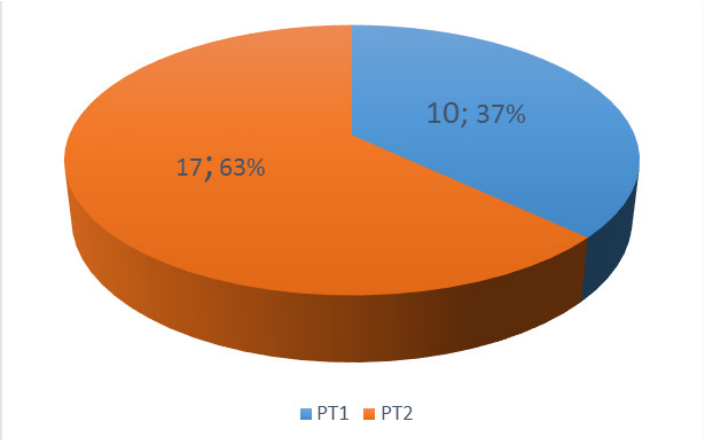

Chart 1. Primary tumor stage distribution for SEM

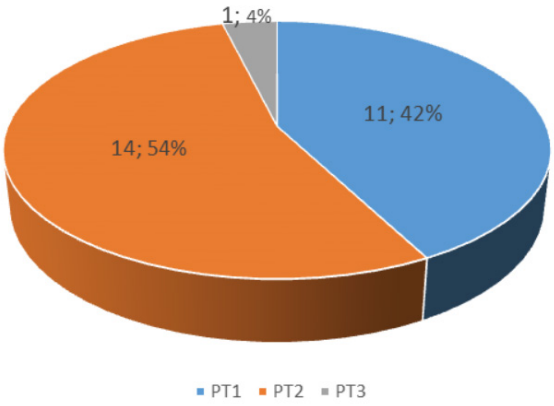

Chart 2. Primary tumor stage distribution for NSE-GCT

Table 1. The distribution of the histological characteristics in the SEM and NSE-GCT groups

Histopathological Findings	SEM				NSE-GCT				p value
	Positive		Negative		Positive		Negative		
	n	%	n	%	n	%	n	%	
Intratubular germ cell neoplasia	12	44.4	15	55.6	6	23.1	20	76.9	0.101
Lymphovascular invasion	11	40.7	16	59.3	11	42.3	15	57.7	0.908
Spermatic cord surgical margin	0	0	27	100	0	0	26	100	-
Tumor in the soft tissue surrounding spermatic cord	0	0	27	100	1	3.8	25	96.2	0.491
Rete testis invasion	8	29.6	19	70.4	8	30.8	18	69.2	0.928
Epididymal invasion	6	22.2	21	77.8	7	26.9	19	73.1	0.691
Tunica albuginea invasion	7	25.9	20	74.1	9	34.6	17	65.4	0.491

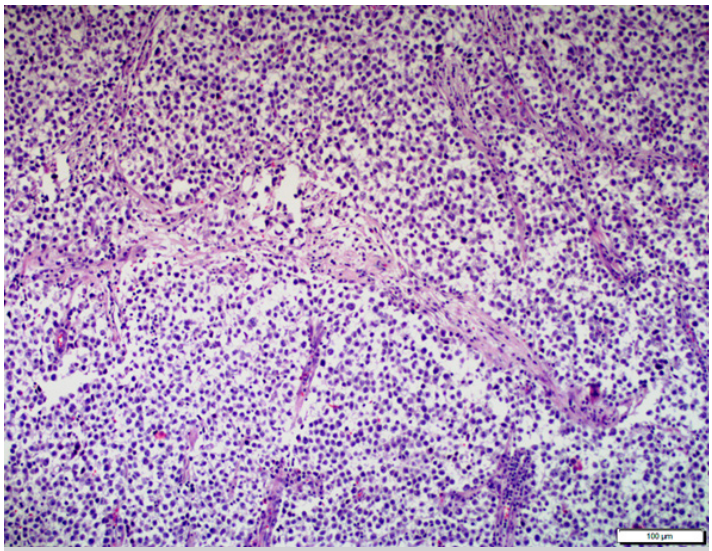

Figure 1. Large round cells with central nuclei, prominent nucleoli and mostly clear cytoplasm in seminoma (H+E, x100)

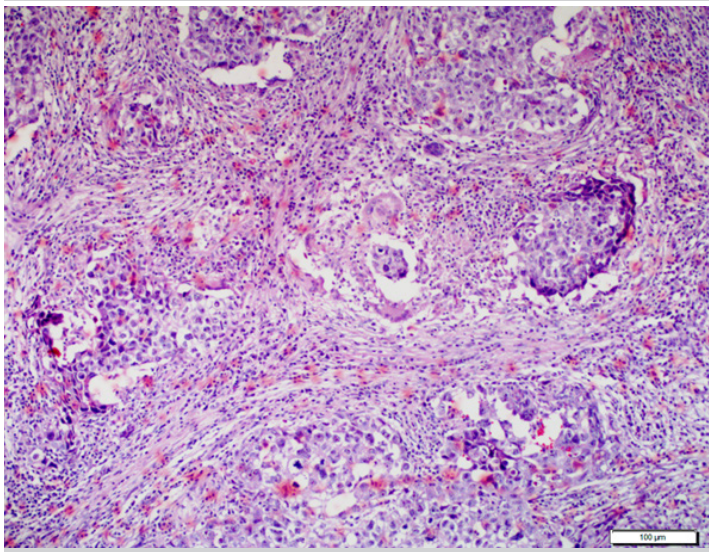

Figure 2. Embryonal carcinomas are characterized by tumor cells organized in sheets, cord or gland-like structures (H+E, x100)

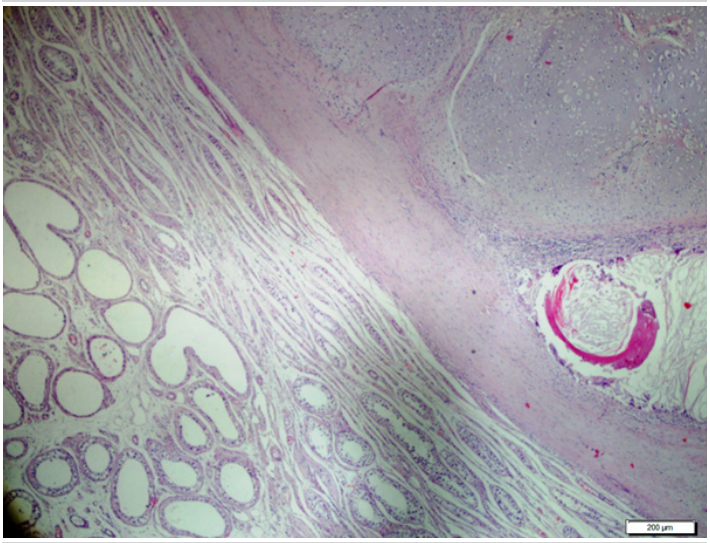

Figure 3. Teratoma component of mixed germ cell tumor (H+E, x40)

DISCUSSION

Germ cell tumors constitute 95% of testicle tumors (1) and they are the most frequently seen tumors in males aged between 20-40 years (1, 5, 6). They make up 10% of the cancer-related deaths in this age group (9). They are rarely seen below 15 years and over 60 years of age (3). NSE-GCTs emerge averagely one decade earlier compared with SEMs; median age at diagnosis is 35-39 years for SEMs whereas median age at diagnosis is 25-29 years for NSE-GCTs (3, 10). Without subgroup discrimination, no patient below 15 years and over 60 years of age was present also in our case series and NSE-GCT was detected at one-decade earlier age compared with SEM consistently with the literature. It has been shown in the studies that their incidence has increased in the recent half century because of lifestyle changes (11) and varies between racial/ethnic groups (5, 10, 12, 13). The incidence of germ cell tumors in the Scandinavian and European countries is higher compared with the Asian and African countries. Their incidence in the Scandinavian countries is 9.9/100.000 whereas that value was detected to be 1.3-4/100.000 in the region including Turkey, mortality rates of germ cell tumors in those regions were 0.27/100.000 and 0.53/100.000, respectively (14). These variations in its incidence and mortality rates result from the differences between the populations with respect to the factors (genetic and environmental) that increase testicular cancer (10). Its most common presentation form is painless mass or swelling in the testicle (9). All the cases in our series had applied to the hospital due to the complaint of palpable mass in the scrotum and these masses were painful in 10 patients. Approximately 2-3% of the testicular tumors are bilateral and they are more frequently identified in the right testicle compared with the left testicle depending on the frequency of undescended testicle (1, 15). Bilateral testicular tumors usually have the same histological structure; the most frequently seen bilateral tumor is SEM (6). Consistently with the literature, without subgroup discrimination, 30 (%57) of the tumors were located at the right testicle in this study and bilaterality rate was 2%. The only bilateral case had morphology of SEM. Nevertheless, it has been also reported in some studies that TGCTs were encountered in both testicles with an equal rate whereas SEMs are more frequently located at the left testicle (16, 17). In our case series, SEMs were detected in the right and left testicles with an equal rate.

TGCTs are histologically divided into two groups as SEM and NSE-GCT, half of the cases show the morphology of SEM. Yolk sac tumor (YST), embryonal carcinoma (EC), choriocarcinoma (CC), teratoma (TE) and mixed germ cell tumor (MGCT) are the tumors classified under the title of NSE-GCT. MGCTs are classified under the title of NSE-GCT independently from the SEM component that they contain. MGCTs are the most commonly seen group among NSE-GCTs and they demonstrate the morphological combinations of EC+TE, EC+SEM or EC+YST

while they may have any morphological combination; they commonly include more than 2 components (7). It has been shown in some studies that MGCT is the most frequently seen subtype among NSE-GCTs (1, 13, 16). Consistently with the literature, 51% and 49% of our cases were in the SEM and NSE-GCT groups, respectively, and 69.2% of the NSE-GCTs revealed the morphology of MGCT. Nevertheless, there are also some studies that have reported YST as the most prevalent subtype (18). It was detected no pure YST in this study.

The most important factors that influence the selection of the appropriate treatment option and treatment decision-making in the follow-up period are TNM stage and the levels of the serum biomarkers (19). In the literature, the levels of serum biomarkers were found high in approximately 90% of the NSE-GCT cases whereas this rate is nearly 30% for SEM (20, 21). Differently from the literature, high levels of serum biomarkers, predominantly high levels of LDH, were detected in over 85% of the cases in the SEM group. It was concluded that some amount of bigger tumor sizes in the SEM group compared with the NSE-GCT group was one of the reasons of this difference. Another reason may be a missing value of 10% that might have created a selection bias. Although, different immunohistochemical markers also have been identified in the literature, tumoral biomarkers are still important in determination of prognosis. However, high levels of AFP and ß-HCG were encountered not only in the germ cell tumors, but also other tumor types manifested the high levels of these markers since increased ß-HCG levels have been monitored in the neuroendocrine tumors, kidney, lung, head and neck cancers, urinary bladder and GI systems while increased AFP levels were detected in the liver diseases. On the other side, LDH is not specific for TC and elevated LDH levels may be identified in both benign and malignant forms of different diseases (22, 23).

Limitations of the study

The most important limitation of the study was the limited sampling size of patients from only a single center. A second limitation was the lack of data related with comorbidities and follow-ups of the patients.

CONCLUSION

Testicular cancers are the most frequently seen malignancies in the young males and their incidence has increased in the recent years. The most important factors that affect the selection of the appropriate treatment option and treatment decision-making in the follow-up period are TNM stage and levels of the serum biomarkers. The complete cure rate is approximately 100% thanks to early diagnosis as well as high chemosensitivity and radiosensitivity of these tumors.

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Peer-Review

Externally Peer Reviewed

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

The study was approved by Non-invasive Clinical Research Ethics Committee of Hatay Mustafa Kemal University (with date 04.06.2020, and number:32, and Helsinki Declaration rules were followed to conduct this study.

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