■ ONCOLOGY

Adjacent venous tumour thrombus in primary osteosarcoma of the pelvis and limbs

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Aims

Venous tumour thrombus (VTT) is a rare finding in osteosarcoma. Despite the high rate of VTT in osteosarcoma of the pelvis, there are very few descriptions of VTT associated with extrapelvic primary osteosarcoma. We therefore sought to describe the prevalence and presenting features of VTT in osteosarcoma of both the pelvis and the limbs.

Methods

Records from a single institution were retrospectively reviewed for 308 patients with osteosarcoma of the pelvis or limb treated between January 2000 and December 2022. Primary lesions were located in an upper limb (n = 40), lower limb (n = 198), or pelvis (n = 70). Preoperative imaging and operative reports were reviewed to identify patients with thrombi in proximity to their primary lesion. Imaging and histopathology were used to determine presence of tumour within the thrombus.

Results

Tumours abutted the blood vessels in 131 patients (43%) and encased the vessels in 30 (10%). Any form of venous thrombus was identified in 31 patients (10%). Overall, 21 of these thrombi were determined to be involved with the tumour based on imaging (n = 9) or histopathology (n = 12). The rate of VTT was 25% for pelvic osteosarcoma and 1.7% for limb osteosarcoma. The most common imaging features associated with histopathologically proven VTT were enhancement with contrast (n = 12; 100%), venous enlargement (n = 10; 83%), vessel encasement (n = 8; 66%), and visible intraluminal osteoid matrix (n = 6; 50%). Disease-specific survival (DSS) for patients with VTT was 95% at 12 months (95% CI 0.87 to 1.00), 50% at three years (95% CI 0.31 to 0.80), and 31% at five years (95% CI 0.14 to 0.71). VTT was associated with worse DSS (hazard ratio 2.3 (95% CI 1.11 to 4.84).

Conclusion

VTT is rare with osteosarcoma and occurs more commonly in the pelvis than the limbs. Imaging features suggestive of VTT include enhancement with contrast, venous dilation, and vessel encasement. VTT portends a worse prognosis for patients with osteosarcoma, with a similar survivability to metastatic disease.

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Introduction

Venous tumour thrombus (VTT) is a rare finding in primary bone sarcomas. Reports of VTT in bone sarcoma are limited, and most of the available literature focuses on sarcomas of the pelvis, with osteosarcoma being most commonly associated with VTT.[1] Estimates of the incidence of VTT in pelvic osteosarcoma range from 15% to 51%.[1-3] Tumour thrombus is a negative prognostic factor in osteosarcoma of the pelvis and therefore early recognition of VTT is key.[1,4] Vascular invasion also poses a challenge with margin-negative resection, so preoperative detection of VTT is necessary for appropriate surgical planning.

Despite the high rate of VTT in osteosarcoma of the pelvis, there are few descriptions of VTT associated with extrapelvic primary osteosarcoma. Most of the existing reports describe tumour thrombus distant to the primary tumour, which may represent metastatic disease rather than a

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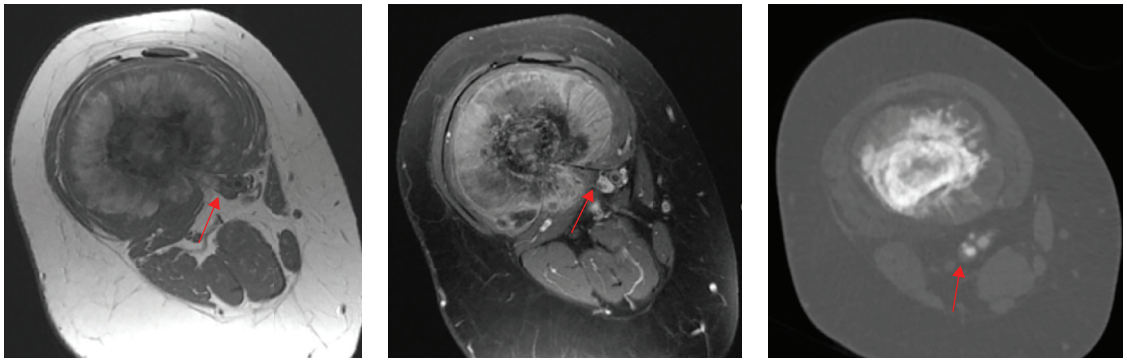

a b c

Fig. 1

a) Axial T1-weighted MRI of distal femur osteosarcoma with popliteal vein thrombus (red arrow). b) Axial contrast-enhanced T1-weighted MRI demonstrating enhancement of the thrombus with gadolinium. c) Axial contrast-enhanced CT of the same patient demonstrating osteoid matrix within the popliteal vein, later confirmed by histopathology to be tumour thrombus.

locally advanced yet resectable lesion with adjacent tumour thrombus.[5,6] Articles describing adjacent VTT in osteosarcoma of the limb are limited to a few case reports, and data on its prevalence are absent.[3,7] We therefore sought to describe the prevalence and presenting features of VTT in osteosarcoma of both the pelvis and the limbs.

Methods

Following institutional review board approval, the medical records for patients treated for osteosarcoma between January 2000 and December 2022 were retrospectively reviewed. Patients with primary lesions of the pelvis or limbs were included for analysis. Patients with unknown primary sites or without cross-sectional imaging prior to surgical intervention were excluded from this study, as were patients with histological low-grade tumours. Clinical documentation, operative notes, pathology reports, and radiological images were screened for patients diagnosed with any form of venous thrombus during or prior to resection of primary osteosarcoma. Cross-sectional imaging in the form of MRI and/or CT scan was reviewed to characterize features of both bland (uninvolved by tumour) and tumour thrombi as well as the relationship to the nearby vascular structure. Vascular abutment was defined as the absence of a clear soft-tissue plane between the tumour and the vessels spanning less than 180° of the vessel circumference. Encasement was defined as greater than 180° of circumferential interface between the tumour and vessels. For patients whose thrombi were discovered intraoperatively, preoperative imaging was reviewed to determine the features of the missed thrombus.

Diagnosis of osteosarcoma was verified by bone and soft-tissue pathologists at our institution. All patients were treated with neoadjuvant chemotherapy. All chronological endpoints, including length of follow-up, time to recurrence, and time to death, were measured from the date of diagnostic biopsy. All patients with VTT were followed for a minimum of 12 months or until death.

In total, 308 patients with osteosarcoma of the pelvis or limb met criteria for inclusion after excluding those without preoperative imaging (n = 31), non-pelvic axial tumours (n = 11), and unknown primary site (n = 1). Mean age of the included cohort was 20 years (SD 25) and 46% of patients were female (n = 143). Primary lesions were located in the upper limb (n = 40), lower limb (n = 198), or pelvis (n = 70).

Statistical analysis. Length of follow-up, time to recurrence, and time to death were measured from the date of diagnostic biopsy. Categorical variables were described as frequency and percentages, and continuous variables are described as mean and SD. Pearson's chi-squared test was used to compare categorical variables. A p-value < 0.05 was considered significant. Disease-free survival estimates were calculated using the Kaplan-Meier method. Statistical analysis was completed using the BlueSky Statistics software package v. 7.40 (BlueSky Statistics, USA).

Results

In our series of 308 patients, 47 patients (15%) had distant metastases on presentation. Primary tumours abutted the blood vessels on preoperative imaging in 131 patients (43%). Vessels were circumferentially encased in 30 of 308 patients (10%). Lesions of the pelvis were more likely to abut (57% (40/70) vs 39% (54/138); odds ratio (OR) 2.12 (95% CI 1.23 to 3.68)) and encase (26% (18/70) vs 6% (8/138); OR 5.69 (95% CI 2.60 to 12.5)) a nearby major vascular bundle compared to lesions of the limb.

In total, 24 patients with pelvic osteosarcoma (35%) and seven patients with limb osteosarcoma (3%) were found to have some form of venous thrombus adjacent to their primary tumour. The vast majority of thrombi were detected on imaging (n = 27), and the remainder were discovered intraoperatively (n = 4). In all, 21 cases of thrombus were determined to be involved by tumour based on histopathological analysis (n = 12) or characteristic imaging features (n = 9). Comprehensive details can be found in Table I. The remaining ten cases of venous thrombus were considered to be bland thrombi based on pathology (n = 1), imaging features alone (n = 7), or resolution with therapeutic anticoagulation (n = 3).

Table I. Patients with venous tumour thrombus in osteosarcoma of the pelvis and limbs.

Patient	Age, yrs	Sex	Primary site	Distal extent of tumour thrombus	Mode of detection	Metastases on presentation	Chemo	Local control	Recurrence/ relapse	Follow-up
1	16	F	Femur	Femoral vein	Intraoperative pathology	No	Yes	Limb salvage	Local, 3 yrs	DOD, 6 yrs
2	16	F	Pelvis	External iliac vein	MRI	Yes, lung	Yes	Internal hemipelvectomy	Local, 1.5 yrs	DOD, 3 yrs
3	47	M	Pelvis	Internal iliac vein	Intraoperative pathology	No	Yes	Definitive radiation*		DOD, 2 yrs
4	16	F	Pelvis	Small vein near common iliac	Intraoperative pathology	No	Yes	External hemipelvectomy		ANED, 12 yrs
5	27	F	Pelvis	Internal iliac vein	CT angiogram	No	Yes	External hemipelvectomy		ANED, 6 yrs
6	25	F	Femur	Femoral vein	Ultrasound	Yes, lung	Yes	Amputation		ANED, 13 yrs
7	48	F	Femur	Popliteal vein	MRI, CT angiogram	No	Yes	Hip disarticulation		ANED, 4 yrs
8	18	F	Tibia	Common femoral vein	Intraoperative pathology	No	Yes	Hip disarticulation	Distant (lungs), 6 mths	AWD, 13 mths
9	65	M	Pelvis	Common iliac vein	MRI	Yes, lung	Yes	Palliative radiation		DOD, 14 mths
10	19	M	Pelvis	Common iliac vein	CT with contrast	No	Yes	External hemipelvectomy	Local, 4 mths	DOD, 2.5 yrs
11	16	M	Pelvis	Common iliac vein	MRI	No	Yes	Definitive radiation		DOD, 4 yrs
12	17	M	Pelvis	Common iliac vein	MRI	No	Yes	Internal hemipelvectomy		DOD, 15 mths
13	16	F	Pelvis	Internal iliac vein	MRI	No	Yes	Definitive radiation		DOD, 3 yrs
14	17	F	Pelvis	Internal iliac vein	MRI	No	No†	None		DOD, 5 mths
15	23	M	Pelvis	Superior gluteal vein	MRI, CT angiogram	No	Yes	Definitive radiation	Distant (lungs), 21 mths	AWD, 3 yrs
16	16	M	Pelvis	Internal iliac vein	CT angiogram	No	Yes	Total sacrectomy		ANED, 14 mths
17	36	M	Pelvis	Internal iliac vein	MRI, MR angiogram	No	Yes	External hemipelvectomy	Local, 20 mths	DOD, 3 yrs
18	31	M	Pelvis	Internal iliac vein	CT angiogram	No	Yes	Definitive radiation		DOD, 2.5 yrs
19	53	M	Pelvis	Internal iliac vein	MRI	No	Yes	Definitive radiation	Distant (lungs), 4 mths	AWD, 14 mths
20	30	F	Pelvis	Superior gluteal vein	MRI, CT angiogram	Yes, lung	Yes	None		DOD, 3 yrs
21	15	M	Pelvis	Superior gluteal vein	MRI	No	Yes	Definitive radiation	Distant (lungs), 12 mths	AWD, 4 yrs

*Resection aborted intraoperatively upon discovery of extensive tumour thrombus.
†Patient died of disease prior to initiation of chemotherapy.
ANED, alive with no evidence of disease; AWD, alive with evidence of disease; DOD, died of disease.

The overall rate of VTT in pelvic osteosarcoma was 25% (n = 17), which was significantly higher than the rate of VTT in limb osteosarcoma (2% (n = 4); OR 18.5 (95% CI 5.7 to 78.9)). Four of these patients had distant metastases on presentation. Histological subtype consisted of chondroblastic osteosarcoma in 18 patients (86%) and osteoblastic chondrosarcoma in three patients. Treatment consisted of margin-negative resection of the primary tumour in seven patients with pelvic VTT (external hemipelvectomy (n = 4), internal hemipelvectomy (n = 2), total sacrectomy (n = 1)) and all patients with limb VTT (internal hemipelvectomy (n = 2), transfemoral amputation (n = 1), wide resection (n = 2)). All surgical excisions included resection of the tumour thrombus. Seven patients were treated with definitive radiation, one of whom had an aborted surgical resection after VTT was discovered intraoperatively.

Imaging features. All histopathologically confirmed VTT demonstrated enhancement with contrast on advanced imaging (Figures 1a and 1b). Ten of these cases (83%) demonstrated enlargement of the vein in the area of thrombus. Osteoid matrix was visible within the thrombus on CT scan in six patients (50%) (Figure 1c). Tumour was noted to abut the vascular bundle in all histopathologically confirmed VTT, with circumferential encasement in two-thirds of these patients (n = 8).

Outcomes. Of the 21 patients with VTT, 11 underwent surgical resection. This includes four patients whose tumour thrombus was discovered intraoperatively. Of the patients with VTT who were treated surgically, only one (9%) had necrosis > 90% following chemotherapy compared to 32% of patients without VTT (p = 0.028, chi-squared test). Five patients were alive with no evidence of disease at final follow-up (median six years (IQR 12.5 to 2.5)), four patients were alive with evidence of disease (median 3 years (IQR 3.5 to 1.0)), and 12 patients died of disease (median 2.5 years (IQR 3 to 1.6)). Four patients developed local recurrence at four months, 18 months, 20 months, and three years following margin-negative resection. Only one of these patients had local recurrence in the area

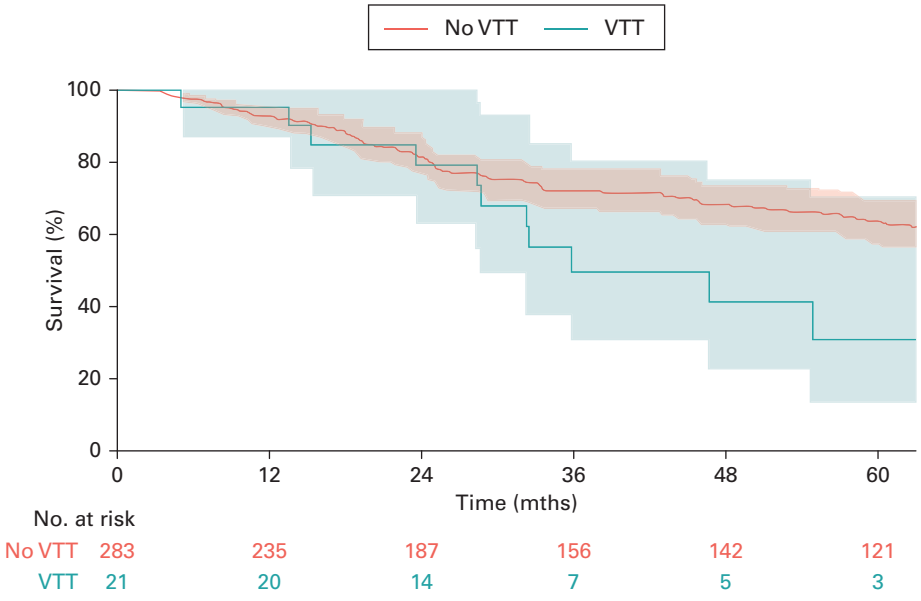

Fig. 2

Kaplan-Meier survival curves of disease-specific survival in patients with and without venous tumour thrombus (VTT) associated with osteosarcoma of the pelvis and limbs.

of the original VTT. All four patients with local recurrence eventually died of their disease.

Disease-specific survival (DSS) for patients with VTT was 95% at 12 months (95% CI 0.87, 1.00; 20 at risk), 50% at three years (95% CI 0.31 to 0.80; seven at risk), and 31% at five years (95% CI 0.14 to 0.71; three at risk) (Figure 2). DSS for patients without VTT was 93% at 12 months (95% CI 0.90 to 0.96; 235 at risk), 72% at three years (95% CI 0.67 to 0.78; 156 at risk), and 64% at five years (95% CI 0.58 to 0.70; 121 at risk). When controlling for presence of metastatic disease, VTT was associated with worse DSS (hazard ratio 2.3 (95% CI 1.11 to 4.84)). There was no difference in DSS between patients with VTT and no metastasis compared with patients with metastases and no VTT (p = 0.184) (Figure 3).

Discussion

VTT in osteosarcoma is poorly understood. Proper recognition of VTT is important for surgical planning as well as prognoses, as studies have found VTT to be associated with worse outcomes in patients with pelvic osteosarcoma.[8–10] The results of the current study highlight the poor prognostic outcome for patients with osteosarcoma and VTT regardless of location and the ability to achieve a negative margin of resection around the thrombus.

In our series, the prevalence of VTT in pelvic osteosarcoma was 25%, which aligns with frequencies reported in the literature.[1,2,4] This was higher than those with limb osteosarcoma. While there have been no other reports on the incidence of VTT in limb osteosarcoma, the relative infrequency compared to pelvic lesions fits with the higher rate of vascular abutment and encasement in this series. Intrapelvic lesions are often detected later than those of the limb, and the resulting increased size and proximity to large vessels may contribute to the higher incidence of VTT compared to the limb.

Survival within the tumour thrombus group was poor. Over two-thirds of patients succumbed to disease within five years despite receiving chemotherapy and surgical resection. This was significantly worse than the five-year survival in patients with localized disease and nearly identical to the five-year survival of patients with metastatic disease at presentation, both of which were comparable to rates in the published literature.[11,12] While the survival curves of non-metastatic osteosarcoma with VTT and metastatic osteosarcoma with VTT are quite similar, our current thinking is that vascular invasion itself does not imply metastatic disease despite gross tumour within the bloodstream. Only four patients in our series presented with metastases (all pulmonary) at the time of tumour thrombus diagnosis, and only three of the remaining 17 patients later developed lung metastases. While not all patients with VTT progress to metastatic disease, the presence of tumour thrombus should increase suspicion of indeterminate lesions downstream of the thrombus, particularly within the lungs for osteosarcoma,[4,13] and further work is needed to determine if the presence of tumour thrombus should be considered in staging algorithms for patients with osteosarcoma. The relatively small sample size in this study poses a challenge for drawing a clear relationship between VTT and survival. Primary tumours located in the pelvis have demonstrably worse outcomes compared to those with limb locations.[8–10] Our series of patients with VTT was predominantly

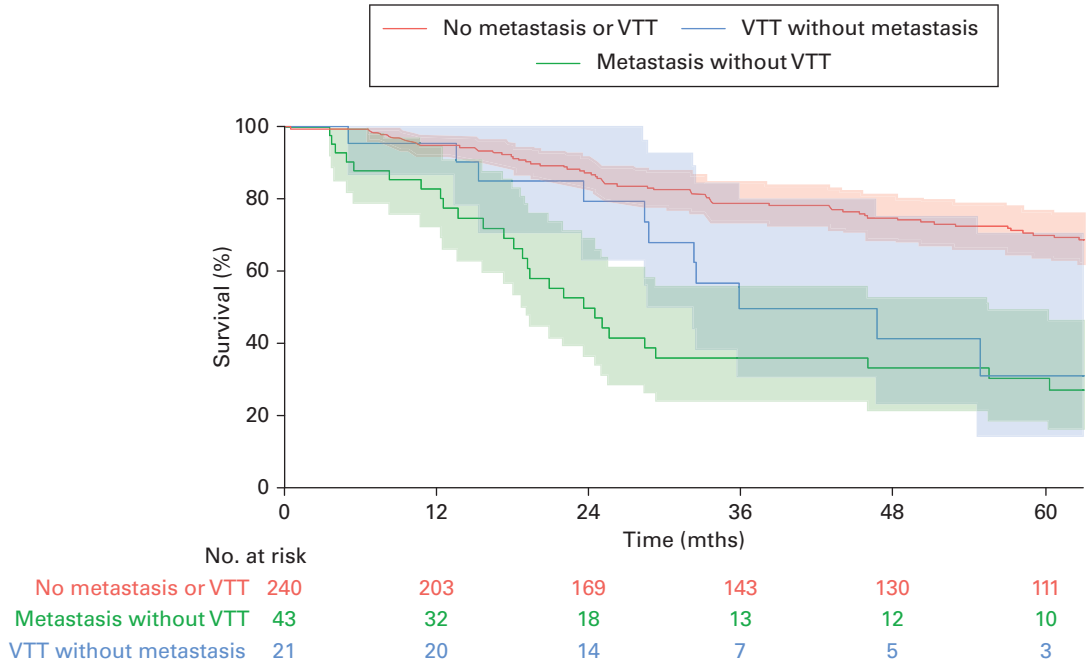

Fig. 3

Kaplan-Meier survival curves of disease-specific survival in patients with venous tumour thrombus (VTT) without metastatic osteosarcoma compared to patients with localized or metastatic osteosarcoma without VTT.

composed of pelvic tumours, which may by related to the lower overall survival rate. Additionally, the majority of the patients in this cohort had chondroblastic histological subtypes, which has been associated with poor response to chemotherapy and worse survival.[14-16]

Four patients in this study had intraoperative discovery of VTT adjacent to the primary lesion. This immediately changed management in two patients – one patient's surgery was aborted upon discovery of extensive thrombus within the internal iliac vein, and the other patient was converted from an above-knee amputation to a hip disarticulation based on the extent of the femoral vein thrombus. None of the intraoperatively discovered VTT were detected preoperatively; however, upon retrospective review of the preoperative imaging for the purposes of this study, three of these lesions were noted to be present on the preoperative imaging. Although preoperative detection of tumour thrombus is optimal for surgical planning, subtle VTT or involvement of small veins may make this difficult, as in these four patients. If margin-negative resection of the primary lesion and VTT is still achievable, excision of intraoperatively discovered VTT is reasonable. However, as occurred in our patient with extensive iliac vein thrombus, the decision to abort surgery may be made if negative margins are not achievable without undue morbidity.

Much of the literature regarding imaging of tumour thrombus is centred on renal cell and hepatocellular carcinoma. There are several agreed features on imaging of vascular filling defects which are concerning for tumour thrombus.[13] These include location within the veins adjacent to or draining the tumour, enhancement with contrast, and dilation of the vein. In addition to these, thrombi of osteoid-producing tumours may demonstrate intraluminal matrix formation. In our series, all histopathologically confirmed tumour thrombi demonstrated enhancement with contrast, and the majority also displayed dilation of the affected vein. Only half of patients with histopathologically confirmed lesions had osteoid matrix within the thrombus that was visible on CT, therefore absence of this finding should not be presumed to exclude tumour thrombus. As most bland thrombi were diagnosed based on absence of these features and without histopathological confirmation, we were unable to assess the sensitivity and specificity of these features in differentiating bland thrombus from tumour involvement. Most patients were treated with therapeutic anticoagulation following discovery of bland thrombi; however, only three patients had subsequent re-imaging following anticoagulation. All three of these cases demonstrated resolution of the suspected bland thrombus.

This study has several primary limitations. The rarity of VTT resulted in a small sample size, which limited statistical analysis, although this is the largest report on VTT associated with limb osteosarcoma in the current literature. While all preoperative cross-sectional imaging was reviewed for the patients in this cohort, subtle tumour thrombus involving small vessels may have gone undetected and therefore the true incidence of these lesions is probably underestimated. Additionally, in all but one case of bland tumour thrombus, clots were determined to be uninvolved by tumour based on imaging alone, which may contribute to underestimation of the incidence of VTT given that histopathological examination is the reference standard for evaluation of tumour involvement.

In conclusion, we present a cohort of patients with tumour thrombi of osteosarcoma of the limbs and pelvis. Our report contributes to the sparse literature on VTT in osteosarcoma and highlights the need for further investigation with multi-institutional collaboration to characterize the true implications of these lesions. Although VTT in osteosarcoma is rare, clinicians should be aware of the possibility, and use the results of this study to inform conversations with patients regarding prognosis and risk of recurrence.

Take home message

- Venous tumour thrombus is rare with osteosarcoma and portends a worse prognosis for patients with a similar survivability to metastatic disease.

Social media

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Data sharing:
The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

Ethical review statement:
This study was approved by our Institutional Review Board (ID: 22-007659).

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