Case Report

Successful treatment of advanced alveolar soft part sarcoma with camrelizumab combined with apatinib: a case report

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Abstract: Alveolar soft part sarcoma (ASPS) is a rare and highly malignant mesenchymal tumor that primarily affects adolescents and young adults. ASPS is characterized by a slow growth rate, high metastatic potential, and resistance to conventional therapies. The emergence of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of advanced malignancies, improving the objective response rate (ORR) and prolonging patient survival. The combination of immunotherapy with targeted therapies can overcome resistance to treatment with ICIs alone. Although substantial progress has been made in various solid tumors, the clinical relevance of ICIs, used alone or in combination with other therapies, in patients with ASPS remains unclear. This is a case report of a 32-year-old man who was diagnosed with advanced ASPS. After 8 months of anlotinib treatment, the patient's disease progressed and new cerebellar metastases were detected. Radiotherapy was administered in addition to camrelizumab combined with apatinib to treat the brain metastases. The patient achieved partial remission (46%) after 3 months of treatment and did not present any severe side effects. This is the first reported case of the successful treatment of advanced ASPS with camrelizumab combined with apatinib. This case supports the use of a novel treatment regimen for patients with inoperable ASPS or ASPS that is resistant to conventional therapies.

Keywords: Alveolar soft part sarcoma (ASPS); immunotherapy; camrelizumab

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Introduction

Alveolar soft part sarcoma (ASPS) was first described by Christopherson and Stewart in 1952 as a rare type of soft tissue malignancy (1). ASPS comprises only 0.5–1.0% of all soft tissue sarcomas (2), and predominantly affects young individuals aged between 15 and 35 years old. In children, ASPS primarily affects the head and neck (2,3), while in adults it typically occurs in the deep soft tissues of the limbs and body trunk, especially in the upper and lower extremities (2). In contrast to other sarcomas, ASPS is characterized by inert growth and a high incidence of distant metastasis (4). In fact, the majority of ASPS patients present with distant metastases at the time of diagnosis, with the lungs being the most common metastatic site (42%), followed by the bones (19%), brain (15%), and lymph nodes (7%) (2).

The most effective treatment for patients with early-stage ASPS is radical surgical excision of the primary tumor (2). However, the therapeutic options for patients with advanced disease are limited by the resistance of ASPS to radiotherapy and chemotherapy (2,5). In fact, conventional chemotherapy has a complete or partial response rate of less than 10% (2). As a consequence, the prognosis of patients with advanced or metastatic ASPS is extremely poor (5,6). Therefore, the development of novel and more effective therapeutic methods for the treatment of ASPS is of high clinical importance.

The tyrosine kinase inhibitor (TKI) apatinib has been

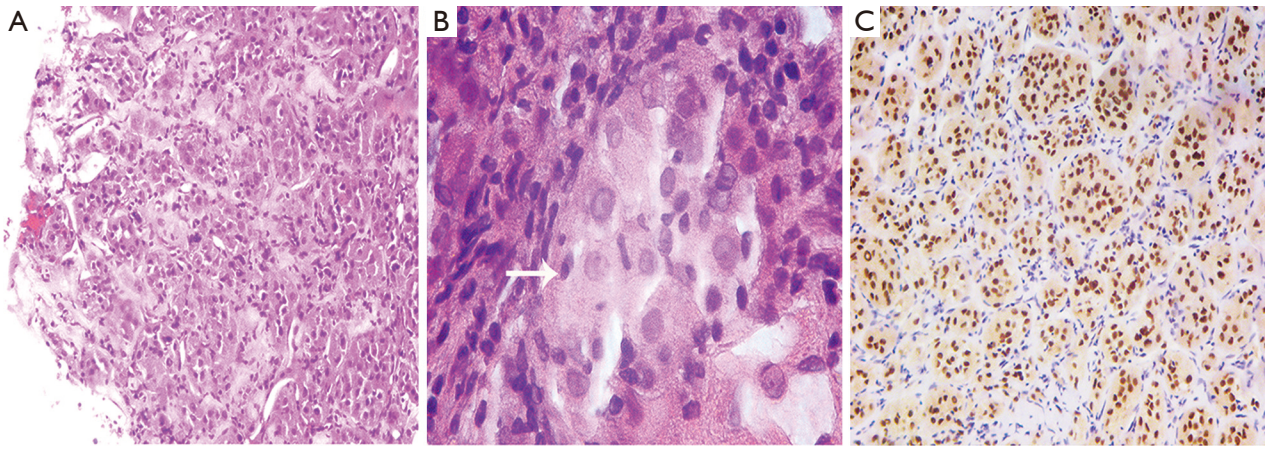

Figure 1 Alveolar soft part sarcoma in a 32-year-old male. (A) Hematoxylin and eosin (H&E) staining showing a nested growth pattern in tumor cells (magnification ×100). (B) Typical periodic acid-Schiff (PAS)-positive particles were observed in the cytoplasm of neoplastic cells (white arrow). The cell nucleoli were large and eccentric (H&E; magnification ×400). (C) Representative immunohistochemical staining (IHC) image showing strong nuclear TFE3 expression in alveolar soft part sarcoma (ASPS) cells (IHC; magnification ×100).

shown to exert potent anti- angiogenic and anti-tumor effects (7,8). Moreover, camrelizumab, a newly developed humanized programmed cell death 1 (PD-1) monoclonal antibody, binds to PD-1 with high-affinity, blocking the PD-1 pathway on T cells, thereby unleashing a cascade of anti-tumor immune responses (6,9,10). It has been reported that the combination of these two drugs exerts a synergistic effect while maintaining a favorable safety profile (8).

This is a case report of a 32-year-old male with advanced ASPS and multiple organ metastases who showed a strong response to treatment with the combination of camrelizumab plus apatinib. Follow-up imaging after six treatment cycles revealed that both the primary tumor and metastatic lesions had regressed. The patient's vital signs were stable, and his quality of life was improved.

We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2275).

Case presentation

A 32-year-old male presented to the hospital with hemoptysis in July, 2018. Computed tomography (CT) examination revealed multiple bilateral lung metastases, as well as a pancreatic lesion (size: 2.8 cm × 2.9 cm × 2.4 cm) which was biopsied. Patient has former cigarette smoking history of at least 15 years. No family history was identified. Microscopically, a nested growth pattern was observed, in which the diffusely distributed tumor cells were uniform in size and shape, and surrounded by fibrous blood vessels (*Figure 1A*). Typical periodic acid-Schiff (PAS)-positive particles were observed in the cytoplasm, and the cell nucleoli were large and eccentric (*Figure 1B*). Immunohistochemical staining (IHC) indicated strong positive expression of nuclear TFE3 (*Figure 1C*).

Since ASPS very rarely develops in the pancreas, investigations were conducted to determine the location of the primary tumor. A positron emission tomography (PET-CT) scan revealed that the primary tumor was in the right thigh (size: 4.1 cm × 4.4 cm; maximum standardized uptake value: 8.9; *Figure 2A*). Hence, the patient was diagnosed with stage IV ASPS originating from the right femur [clinical stage T1N0M1 as per the American Joint Committee on Cancer (AJCC) staging system, 8th edition]. Since surgery is not recommended for advanced ASPS patients, the patient was prescribed the TKI anlotinib (12 mg, from day 1 to day 14, repeated every 21 days). After 8 months of anlotinib treatment, the patient developed grade 1 liver damage, and new metastases were detected on the right cerebellum (size: 2.0 cm × 1.5 cm). As a result of this, the administration of anlotinib was discontinued.

The patient's brain metastases were treated with radiotherapy, using a total dose of 60 Gy, given at 2-Gy fractions, five times per week. The patient also underwent six cycles of a different TKI, apatinib (450 mg, once daily), combined with camrelizumab (200 mg, every 2 weeks). After 3 months of treatment, the patient achieved partial remission (46% from baseline; *Figure 2B,C,D,E*) based on the Response

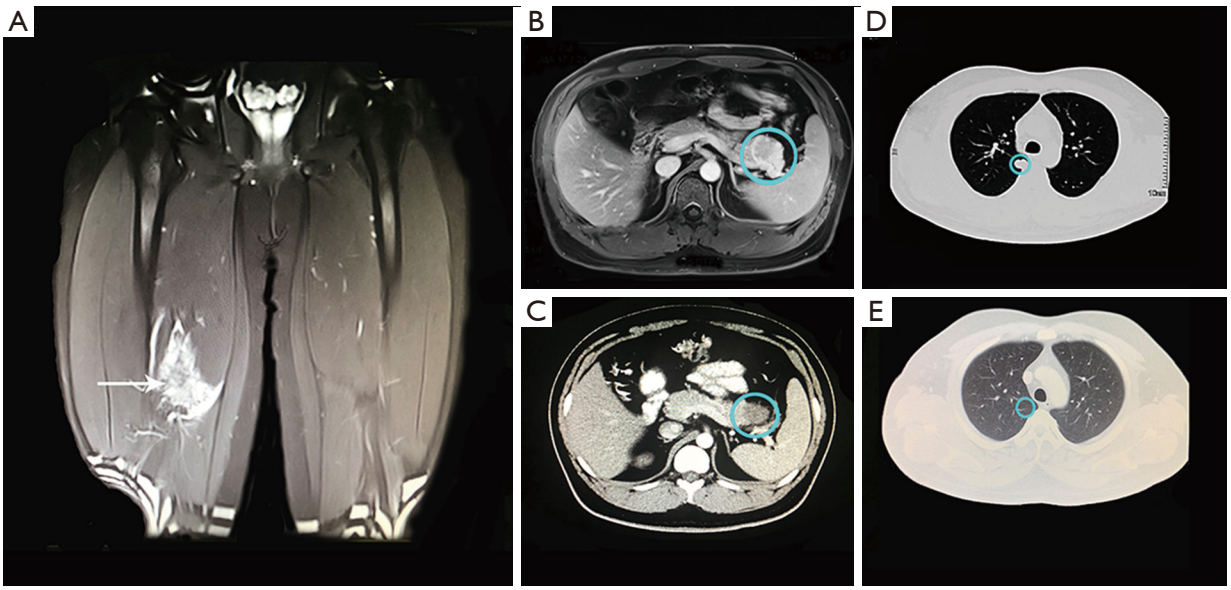

Figure 2 Imaging evaluation of apatinib combined with camrelizumab antitumor activity. (A) T2 arterial phase magnetic resonance imaging showing the primary alveolar soft part sarcoma (ASPS) tumor in the right anterior thigh (white arrow). (B) T2-weighted MRI showing the pancreatic lesion (blue circle). (C) Contrast-enhanced computed tomography (CT) scan showing regression of the pancreatic lesion 4 months after the combination therapy. (D) Right lung metastases (blue circle) before treatment. (E) Contrast-enhanced CT scan showing tumor regression in the lung after six cycles of combination therapy.

Evaluation Criteria in Solid Tumors (RECIST) version 1.1. After 6 months of treatment, the tumor regression continued with a 69% decrease from baseline. During the course of treatment, the patient experienced grade 1 bone marrow suppression (neutrophil granulocyte count was 0.63×10^9/L in the first cycle of treatment), which improved after symptomatic treatment. A follow-up was conducted every 3 months, including physical examination, enhanced CT of the chest, abdomen and lower extremities, enhanced MR of the brain and serum tumor markers. The patient is still receiving treatment and to date we have not observed treatment related side effects. Followed up to October 2020, the patient showed sustain partial remission for 10 months, and his life satisfaction is improved (*Figure 3*).

Written informed consent was obtained from the patient for publication of this study and any accompanying images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Discussion

ASPS is an extremely rare and highly malignant soft tissue tumor. It is characterized by a relatively slow growth rate, high metastatic potential, and a high likelihood of recurrence (11). Typically, ASPS is insidious in its onset, commonly manifesting as a painless mass (11). Often, patients initially present with hemoptysis or headaches. The lack of distinct symptoms hampers early detection, resulting in a high frequency of missed diagnosis and misdiagnosis. The blood-rich nature of ASPSs often leads to hematogenous spread and subsequent distant metastases in the early stages of the disease (6). In fact, pulmonary or brain metastases are detected during the initial diagnosis in 33% of ASPS patients (11). The vast majority of patients diagnosed with pulmonary metastasis also develop metastases in other distant organs (12). Pathological diagnosis remains the gold standard for ASPS. The histological features of ASPS are unique. The polygonal tumor cells are separated by thick fibrous septa, forming uniform-sized lobules (13). The tumor cells have eosinophilic cytoplasm, which contains diamond-shaped or needle-like PAS crystals (14). Additionally, most ASPSs are positive for nuclear TFE3 expression (13).

Previous cytogenetic studies have demonstrated the involvement of chromosomal abnormalities in ASPS (15). Notably, the unbalanced translocation der(5)t(X;17)

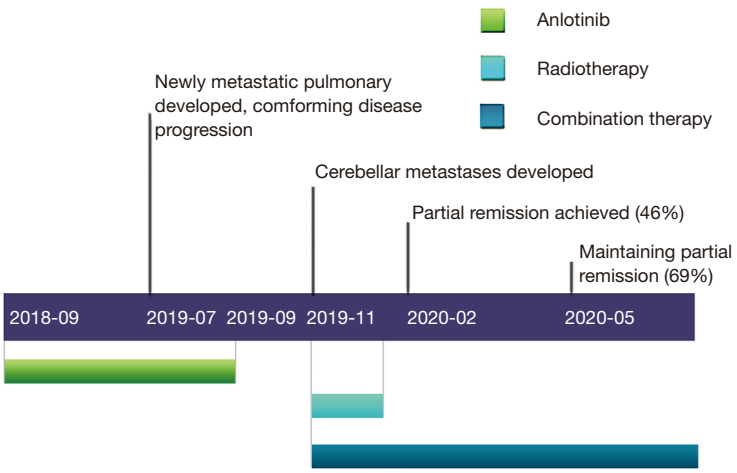

Figure 3 Treatment process timeline, illustrating the application of drugs and the state of disease during treatment.

(p11.2;q25) is frequently detected in ASPS patients, and results in the transfusion of the TFE3 gene with ASPL (15). The transcripts expressed by the ASPL-TFE3 fusion gene can induce aberrant cell proliferation along with the secretion of angiogenesis-promoting factors, such as neurite growth-promoting factor 2 (NEGF2) and Jagged-1 (JAG1). These factors contribute to the high vascularization and metastatic potential of ASPS (16,17).

Although ASPS is a relatively inert sarcoma, clinical evidence has shown that it is resistant to radiotherapy and chemotherapy (11). Despite the use of anti-angiogenic agents, such as apatinib, bevacizumab, and sunitinib, in the treatment of metastatic ASPS, tumor recurrence is inevitable (14). Ultimately, the prognosis of ASPS is poor, and patients often die from complications arising from metastases to vital organs. The overall 5-year survival rate of patients with ASPS ranges from 38–88% (14). For patients without distant metastases, the 5-year survival rate is 60–71%, while metastatic patients have a 5-year survival rate of only 10% (18,19).

Immunotherapy has emerged as a promising therapeutic approach for several malignancies. Notably, antibodies targeting PD-1 and its ligand, PD-L1, have improved the survival rates and quality of life of cancer patients (5). PD-1 is a transmembrane protein that is expressed on the surface of activated immune cells. As PD-1 has a role in mediating inhibitory signals, blocking the interaction between PD-1 and PD-L1 re-activates lymphocytes and restores anti-tumor immune responses (20,21). CTLA-4 blockers can activate tumor-specific T cells by blocking the binding of B7 to CTLA-4 molecules and enhance the anti-tumor immune response (22). Early studies have confirmed that PD-1/PD-L1 more efficient, and the immunosuppressive effect is longer, safer and more reliable (22-24). According to reports in the literature, ASPS PD-1 has a single-agent effective rate of 42–50% (5,25). In a study by Groisberg *et al.*, four ASPS patients were treated with immunotherapy. Partial remission was achieved in 50% of the patients while the other 50% exhibited stable disease (5). Despite the limited number of patients in the latter study, the response rates were promising. The anti-PD-1monoclonal antibody camrelizumab has been approved by the State Drug Administration of China for the treatment of recurrent or refractory classical Hodgkin lymphoma after second-line chemotherapy (26). Despite this, the overall efficacy of PD-1/PD-L1 blockade in the treatment of sarcoma is still inadequate. According to SARC028, a phase II clinical study, the objective response rate (ORR) of immunotherapy in soft tissue sarcoma patients was 19% (27). In the case report presented here, combination treatment with camrelizumab and apatinib resulted in significant regression of the malignant lesions, representing a partial response. Current clinical studies had confirmed the combination treatment of unresectable ASPS already achieved higher response rate, disease control rate, and longer PFS than before. However, the currently researches are mostly case reports, it is insufficient to screen out patient characteristics that benefit from combination therapy of camrelizumab with apatinib. Therefore, large randomized controlled trial should be conducted to examine the potential benefits of

Table 1 Clinical Trials for SHR-1210 combined with apatinib for the treatment of other diseases

Author	Disease	Interventions	Efficacy	PD-L1 expression status and response	Adverse event
Xu J *et al.* (8)	Advanced hepatocellular carcinoma, gastric or esophagogastric junction cancer	SHR-1210 200 mg every 2 weeks and apatinib 125–500 mg once daily	Hepatocellular carcinoma PR 50%, ORR 50%, median PFS 5.8 months; GC/EGJC ORR 17.4%, median PFS 2.9 months	CTCs PD-L1 expression ≥20% 82.9%, <20% 12.2%; CTCs PD-L1 expression ≥20% had a longer median PFS (6.1 *vs.* 2.9 months) and median OS (NR *vs.* 8.9 months)	Grade 3 or 4 AEs 60.6%, mostly hypertension 15.2%, increased aspartate aminotransferase 15.2%
Lan C *et al.* (29)	Advanced cervical cancer	SHR-1210 200 mg every 2 weeks and apatinib 250 mg once per day	ORR 55.6%, CR 4.4%, PR 51.1%, median PFS 8.8 months	PD-L1 positive 66.7%, PD-L1 negative 22.2%	Grade 3 or 4 AEs 71.1%, mostly hypertension 24.4%, anemia 20.0%, fatigue 15.6%
Ren C *et al.* (30)	Metastatic colorectal cancer	SHR-1210 200 mg every 2 weeks and apatinib 250–375 mg once daily	Median PFS 1.83 months, median OS 7.80 months	Not mentioned	Grade 3 AEs 90%, mostly hypertension 30%
Fan Y *et al.* (31)	Extensive-stage small-cell lung cancer	SHR-1210 200 mg every 2 weeks plus apatinib 375 mg once daily	ORR 34.0%, median PFS 3.6 months, OS 8.4 months	PD-L1 expression ≥1% 23.4%, PDL1 <1% 70.2% PD-L1 expression ≥1% had a longer ORR (45.5%: 33.3%)	Grade 3 or 4 AEs 72.9%, mostly hypertension 25.4%, decreased platelet count 13.6%, hand-foot syndrome 13.6%
Xu J *et al.* (32)	Advanced hepatocellular carcinoma	SHR-1210 200 mg (for bodyweight ≥50 kg) or 3 mg/kg (for bodyweight <50 kg) every 2 weeks plus oral apatinib 250 mg daily	The first-line ORR 34.3% median PFS 5.7 months; the second-line ORR 22.5% median PFS 5.5months	Not mentioned	Grade 3 or 4 AEs 77.4%, mostly hypertension 34.2%, increase dgamma-glutamyltransferase 11.6%, neutropenia 11.1%

PR, partial response; CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death-ligand 1; NR not reached; AEs, adverse effects; CTCs, circulating tumor cells

PD-1/PD-L1 blockade, either alone or in combination with other therapies, in the treatment of patients with ASPS.

Although immunotherapy has lower toxicity than traditional chemotherapy, its long-term adverse events (AEs) still cannot be ignored. The long-term AEs are mainly endocrine toxicity. The most common ones are hypophysitis and hypopituitarism (incidence rate 1–10%) (23), followed by gastrointestinal side effects, mostly colitis (grade ≥3 1–5%), ileus, intestinal perforation (28). Compared with CTLA-4, the AEs of PD-1/PD-L1 require long-term monitoring (22). Blood routine examination, liver function, biochemistry index, and thyroid function were recommended every 6–12 weeks within 6 months after the end of treatment. Other hormone levels, such as corticotropin, cortisol should be tested when the patient has fatigue or non-specific symptoms (28). Follow-up frequency should be increased according to individual reactions and AEs.

A number of previous clinical studies have explored the use of SHR-1210 combined with apatinib for digestive system carcinoma, advanced cervical cancer, and extensive-stage small-cell lung cancer (8,29-32) (*Table 1*). Studies by Xu J, Xu JM and others have confirmed that the combination of the two drugs can improve the ORR and long survival of patients with advanced hepatocellular carcinoma (8,32). However, in other studies, the combination of the two drugs for progressive colon cancer, gastric cancer and gastroesophageal junction tumors is not exhaustive (8,32). Patients with PDL1 expression are more likely to benefit from combination treatment, but the relationship between PDL1 expression

level and efficacy is still uncertain (8,23). According to the research of Xu J and Lan C, PD-L1 tumor cell-positive patients are associated with longer PFS, but ORR does not benefit (29,32). Another study has demonstrated that patients with PDL1 positive had better ORR than patients with PDL1 negative (45.5%: 33.3%) (31). In addition to efficacy, safety is also an important factor to be considered in the treatment process. Grade 3 or 4 AEs were observed 60-90%, mostly hypertension 15.2–34.2%, hepohepatia 11.6–15.2%, marrow suppression *et al.* (8,26,30-32). Compared with SHR-1210 monotherapy, the skin capillary hyperplasia symptoms, which is the most common side effect of SHR-1210, were lower than before (67–97%: 3–28.9%) (8,29-33). The mechanism may be related to that apatinib inhibits the VEGFR2 receptor related to vascular endothelial proliferation and blocks angiogenesis (8). Considering the efficacy and tolerability, the dose of SHR-1210 200 mg every 2 weeks and apatinib 250 mg once per day are recommended.

It is worth noting that the efficacy of immunotherapy is positively correlated with the tumor mutation burden (21). ASPS, as a single-type mutant soft tissue tumor, is more sensitive to immunotherapy. However, previous studies observed that PD-L1 was only expressed in 0–2 % of ASPS cells and that the infiltrating immune cells did not express PD-1 (5, 6,29). It is possible that the sensitivity of ASPS to immunotherapy is related to the expression of TFE3, which is involved in the activation of the immune system (16). Future investigations are warranted to provide further insights into the mechanisms underlying the responses of ASPS to immunotherapy.

Our patient is a young male with a history of smoking for 15 years. He was given the standard treatment of SHR-1210 200 mg every 2 weeks and apatinib 250 mg once daily. In the 3rd and 6th months after treatment, the patient's tumor burden was significantly reduced decrease from baseline (46%, 69%). Previous studies have paid more attention to the mechanism of targeted therapy and achieved curative effects. Our patient admitted drug resistance after using anlotinib, apatinib combined with camrelizumab was selected and achieved significant efficacy.

Conclusions

This case study reported an extremely rare ASPS case with metastases in multiple distant organs, including the pancreas. To the best of our knowledge, this case represents the first report of the successful treatment of advanced ASPS with the combination of camrelizumab plus apatinib. The patient's condition improved significantly after treatment, and no adverse side effects greater than grade 3 were observed, thus confirming the favorable safety and efficacy profiles of this treatment regimen. Therefore, the efficacy of this combination treatment in ASPS patients who are resistant to conventional therapies should be further evaluated in large cohort studies.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2275

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2275). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this study and any accompanying images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

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