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Case report

Perivascular epithelioid cell tumor (PEComa) of the uterus: Challenges of pregnancy in determining prognosis and optimal treatment

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A B S T R A C T

Background: Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal neoplasm that exhibits immunohistochemical evidence of smooth muscle and melanocytic differentiation.

Case: We report a case of uterine PEComa in a 21 year-old primigravida, presenting at time of c-section as a small subserosal lesion that expressed soft tan-brown tissue fragments. Microscopically the cells were epithelioid, staining positive for TFE3 and HMB45. Significant cytologic atypia and mitotic activity were concerning for malignancy. The patient was treated post-partum with total robotic hysterectomy and right salpingo-oopherectomy, and is currently without evidence of disease.

Conclusion: This case of PEComa diagnosed during pregnancy highlights the importance of intra-operative biopsy and the difficulty of predicting malignant potential of PEComa in the setting of a gravid uterus with a dynamic smooth muscle architecture.

1. Introduction

Perivascular Epithelioid Cell Tumors (PEComas) are rare mesenchymal neoplasms, which exhibit immunohistochemical expressions of both smooth muscle (SMA, desmin, caldesmon) and melanocytic markers (HMB-45, melan-A, MiTF). PEComas are classically composed of cells with epithelioid appearance and clear or acidophilic cytoplasm with a perivascular distribution (Thway and Fisher, 2015). These tumors have been often confused with smooth muscle tumors, since they share overlapping morphologic and immunohistochemical features. They only received recognition as a subset of soft muscle sarcomas relatively recently.

There are multiple subtypes of PEComas, and they can present in a variety of locations. They include the more common angiomyolipoma (AML), clear cell "sugar" tumor of the lung (CCST), lymphangioleiomyomatosis (LAM), and other unusual clear cell tumors (Thway and Fisher, 2015; Folpe et al., 2005). While many of these can have a benign course, there are certain subtypes such as epithelioid AML and malignant PEComa that are aggressive and can present with metastatic or recurrent disease.

The symptoms of gynecologic PEComas are nonspecific and similar to those of other uterine tumors, often including abnormal uterine bleeding or lower abdominal pain, which may also be present during pregnancy. Here we present the first documented diagnosis of PEComa during pregnancy and review the literature to highlight how to best determine malignant potential of PEComas and determine the appropriate treatment option for this rare disease.

2. Case

Our patient presented as a 21 year-old primigravida at 40 weeks gestational age, with a past medical history remarkable only for a history of Wilm's tumor diagnosed at 12 months of age (treated with right nephrectomy, 6 cycles of adjuvant chemotherapy followed by 9 radiation treatments and surveillance until age 17). The patient's pregnancy itself was uncomplicated, though labor was complicated by fetal intolerance resulting in a primary cesarean section. The fetus was delivered without difficulty, however during closure of the hysterotomy, the surgical team noted what appeared to be a subserosal hematoma superior to the transverse uterine incision. While the team attempted to imbricate the area, the uterus expressed a fleshy, amorphous, tissue from the cavity of this lesion. This tissue was sent to pathology for review. This area was closed primarily, and the remainder of the cesarean section continued in the standard fashion. Her post-operative course was uncomplicated.

The histologic findings of the tissue specimen, which measured 2.5 × 2 × 1 cm, were characterized by an epithelioid appearance of the cells with many mitotic figures. Also present were ganglion-like cells with

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prominent nucleoli and areas of spindling.

Immunohistochemical staining of the tumor cells showed diffuse overexpression of transcription factor E3 (TFE3) and were positive for human melanoma black 45 (HMB45). The cells were negative for S-100, inhibin, EMA, CD34, desmin, SMA, SOX10, and keratin AE1/AE3. Significant cytologic atypia and mitotic activity were present, concerning for malignancy.

Given the dynamic changes in the postpartum myometrium, it was recommended that the patient have an MRI 8 weeks postpartum. MRI revealed a lesion most consistent with a hematoma (4.1 cm × 1.6 × 2.2 cm hypointense lesion that did not enhance with contrast) (Fig. 1). However, PET CT performed the following day showed an ill- defined 4.3 × 3.0 cm hypermetabolic hypoattenuating mass in the lower uterine segment (Fig. 2) as well as a 9 mm area of increased metabolic activity

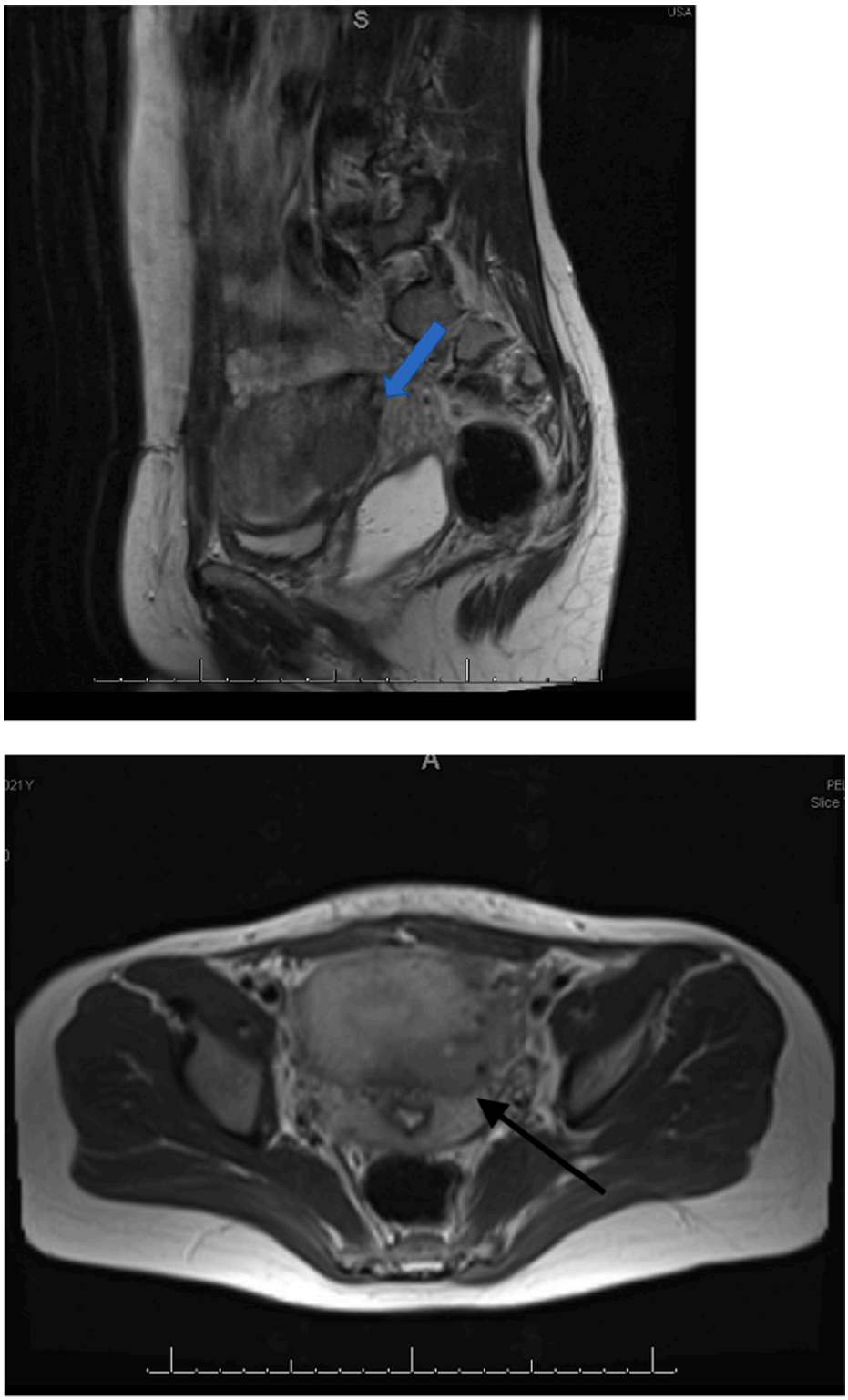

Fig. 1. Sagittal (A) and axial (B) T2 MRI images showing a lesion most consistent with a hematoma, a 4.1 cm × 1.6 × 2.2 cm hypointense lesion that did not enhance with contrast).

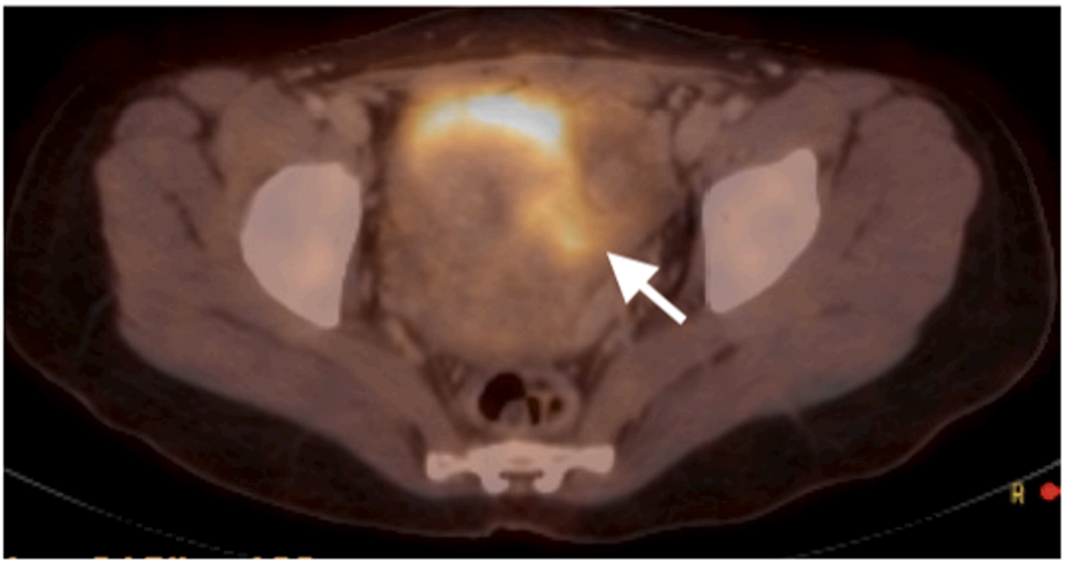

Fig. 2. PET CT showed an ill defined 4.3 cm hypermetabolic, hypoattenuating mass in the lower uterine segment.

lateral to the colon in the right upper quadrant area of the abdomen, suspicious for a peritoneal disease. Given concern for malignancy, hysterectomy with debulking was recommended despite the patient's young age. Approximately 8 weeks following her diagnosis, the patient had a diagnostic laparoscopy with robotic resection of the previously mentioned small bowel implant near the terminal ileum, and hysterectomy with right salpingo-oophorectomy.

At the time of surgery, the uterus had a bulging lower segment that extended into the left broad ligament. A 5.8 × 3.8 × 2.9 cm, irregular soft white–gray mass involving the anterior and posterior myometrium above the lower uterine segment was identified. Microscopically the mass consisted of neoplastic cells with a nested and alveolar architecture and delicate vasculature. The tumor showed a pushing and focally permeative interface with the surrounding myometrium (Fig. 3A). The neoplastic cells displayed a predominantly epithelioid appearance with mild to moderate atypia, clear to granular eosinophilic cytoplasm, and a round nuclei with prominent nucleoli. Focal areas of spindle cell morphology and scattered multinucleated giant cells were also noted (Fig. 3 B). Angiolymphatic invasion was present. The mitotic activity was estimated to be 5 mitosis/50 high power fields. Biopsy of the peritoneal nodule showed a suture granuloma with foreign body reaction, most likely caused by a prior procedure.

Close surveillance was selected over adjuvant treatment with chemotherapy or radiation. The patient was monitored closely with regularly scheduled exams and imaging every 6 months to assess for recurrence. PET CT six months post-operatively showed no evidence of disease. She is currently 3.5 years out from her diagnosis and remains without evidence of disease.

3. Discussion

Here we report one unique case of PEComa diagnosed during pregnancy at the time of a routine cesarean section, confirmed with histopathologic review. Although there was no suspicion for this diagnosis over the course of the pregnancy or prior to delivery, the clinical presentation of gynecological PEComa can be non-specific and diagnosis is difficult to make. There were multiple concerning features for malignancy, so despite the patient's young age decision was made to proceed with definitive surgical treatment.

3.1. Presentation

The peak of incidence of uterine PEComas falls within the 4th to 5th decade of life. The most common signs and symptoms of clinically evident lesions is vaginal bleeding or abdominal pain, making the diagnosis during pregnancy difficult as these symptoms can be present in normal pregnancies. Rarely, they can present with rupture of the uterus or hemoperitoneum, disseminated intravascular coagulopathy, or rarely with a concomitant uterine malignancy (Liu et al., 2019; Musella et al., 2015; Rothenberger et al., 2019; Staley et al., 2015). Small, non-symptomatic tumors are often incidentally discovered. The radiological appearance can be variable and can present as a small benign smooth cell neoplasm or as a large heterogeneous mass.

3.2. Gross findings, histology and tumor markers

Similar to our case, PEComas are often well circumscribed non-encapsulated lesions with a size ranging anywhere from 0.2 to 17 cm (Thway and Fisher, 2015; Bennett et al., 2018). There are classic morphologic and immunohistologic features of these tumors. Morphologically, PEComas demonstrate epithelioid and/or spindled cells with variably clear cytoplasm, variable nuclear pleomorphism, nested or corded architecture, and stromal hyalinization. Supportive immunohistochemical features include: expression of 1 or more myogenic markers (SMA, desmin, h-caldesmon) and 2 or more melanocytic markers (HMB-45, melan-A, MiTF), are characteristic of PEComas (Selenica et al., 2021).

A subset of PEComas harbor *TFE3* gene fusions and show nuclear positivity for *TFE3* by immunohistochemistry, similar to our case. Prior reports indicate that *TFE3*-rearranged PEComas show distinct epithelioid and nested morphology, abundant clear to granular cytoplasm, monotonous nuclei and low mitotic activity (Argani et al., June 2016). In addition to this group, a novel *RAD51B* rearrangement has been described in a subgroup of uterine PEComas (Agaram et al., 2015), as well as in a subset of uterine leiomyomas (Takahashi et al., 2001), expanding the ongoing controversy of neoplasms with overlapping myomelanocytic differentiation.

3.3. Malignant potential

Several algorithms exist to predict the biologic behavior of these tumors. First, Folpe and colleagues in 2005, evaluated a group of soft tissue and gynecologic PEComas based on the presence of several histologic features (Table 1). Three categories were described. High risk criteria include tumor size greater than or equal to 5 cm, infiltrative growth pattern, high nuclear grade cellularity, mitotic rate > 1/50 high

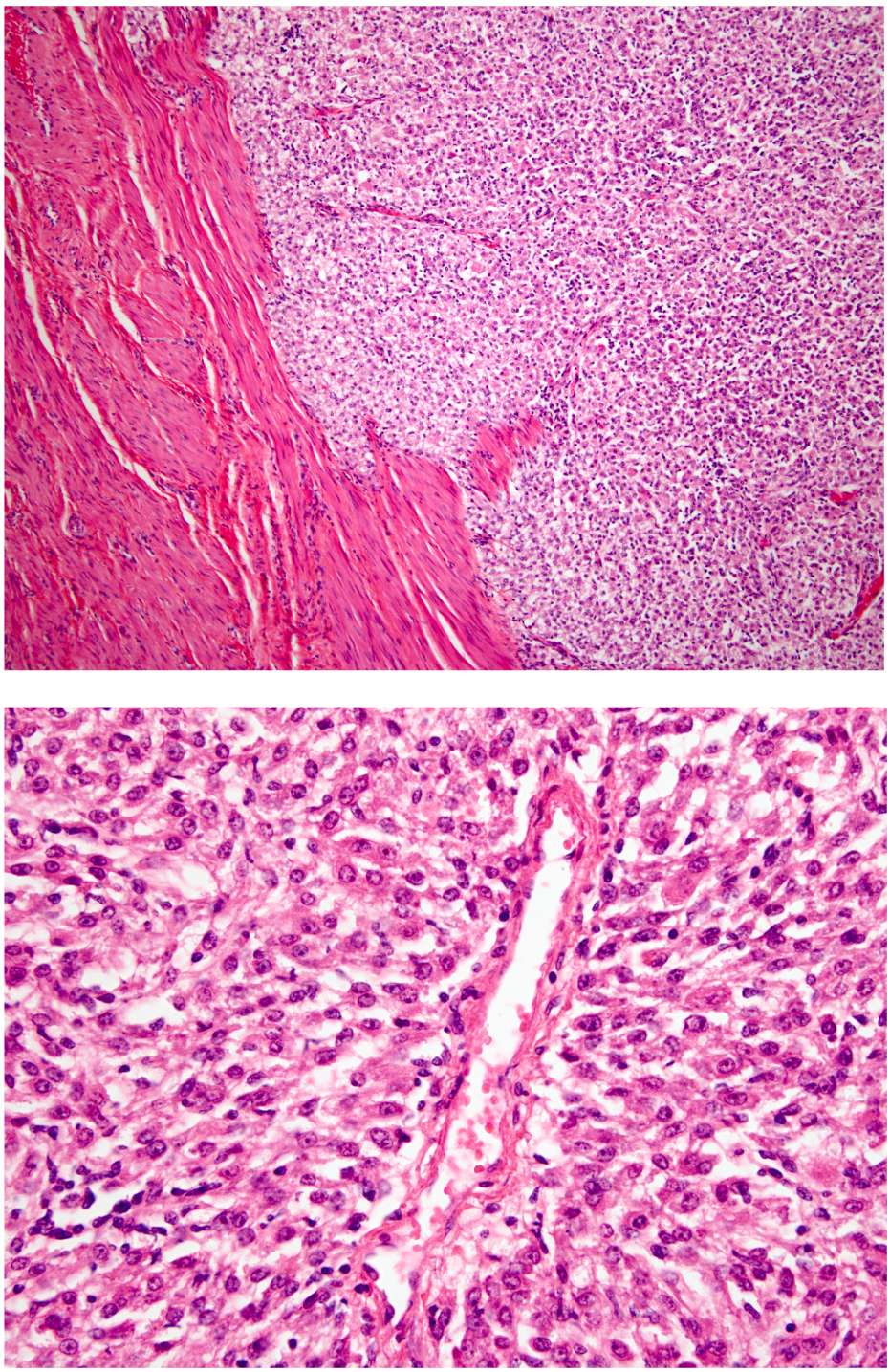

Fig. 3. A. Hematoxylin and eosin stain at 10x showing neoplastic cells with a nested and alveolar architecture with a pushing and focally permeative interface with the surrounding myometrium. B. Slide at 40x shows focal areas of spindle cell morphology and multinucleated giant cells.

power fields, necrosis and vascular invasion. Tumors harboring a single histological feature including nuclear pleomorphism, multinucleated giant cells or size>5 cm are defined as having "uncertain malignant potential". Tumors were labeled as "malignant" if they clearly show 2 or more criteria (Folpe et al., 2005).

Several years later, Schoolmeester and colleagues evaluated a group of 16 PEComas, and reclassified them into benign/uncertain malignant potential and malignant based on the number of atypical features noted (Schoolmeester et al., 2014). A few years later, Bennett proposed the elimination of the benign category after finding recurrence in a case previously classified as benign (Bennett et al., 2018).

Relative to the present case, the molecular and structural changes within the uterus and the endometrium during pregnancy create a challenge when determining the malignant potential of a mesenchymal tumor such as the PEComa. The final diagnosis confirmed 3 concerning features: size>5 cm, high mitotic count and lymphovascular invasion. This validated the decision for surgical management and highlighted the need for continued surveillance.

3.4. Gene pathway and hormonal targets

Most PEComas of various anatomic sites harbor *TSC1/TSC2* gene

Table 1
PEComa classification.

	(Folpe et al., 2005)	(Schoolmeester et al., 2014)	(Bennett et al., 2018)
Benign	*0 worrisome features*	*Less than 4 worrisome features*	
Uncertain malignant potential	*1 or 2 of the following features:* -Nuclear pleomorphism/ multinucleated giant cells only -size > 5 cm		*Less than 3 worrisome features*
Malignant	*2 or more worrisome features*	*4 or more worrisome features*	*3 or more worrisome features*

*Worrisome features:
≥ 5 cm in diameterhigh-grade atypia
(Schoolmeester excludes degenerative atypia)
mitoses > 1/50 HPF
NecrosisLymphovascular invasion
(Folpe includes vascular invasion only)
*HPF = high power field

mutations. These tumor suppressor genes, when mutant, cause a constitutive activation of the mammalian target of rapamycin (mTOR) pathway. Furthermore, recent studies have demonstrated the convergence of the mTOR pathway and estrogen or androgen receptor signaling in PEComas and other malignancies (Gu et al.). These molecular characteristics have led to interest in targeted treatment options.

3.5. Treatment and prognosis

Optimal primary treatment of gynecologic PEComas, especially if localized, appears to be surgical resection of the tumor, usually by way of total hysterectomy with or without bilateral salpingo-oophorectomy. Radical hysterectomy with bilateral salpingo-oophorectomy should be considered in patients with PEComas involving the uterine cervix (Musella et al., 2015).

The role of adjuvant chemotherapy is less clear, mostly due to the rare nature of the disease and lack of sufficient survival and recurrence data. One of the most robust cohorts of patients with locally advanced or metastatic PEComas was studied retrospectively by Sanfillipini and colleagues. Patients were treated with a variety chemotherapeutic agents, often with multiple lines (including anthracycline-based, gemcitabine-based, VEGFR inhibitors and mTOR inhibitors). They found overall response rate (ORR) and progression free survival (PFS) were similar for anthracycline-based regimens and Gemcitabine regimens (20% and 13%, PFS 3.4 and 3.2 months respectively). Anti-angiogenic agents showed only an ORR of 8.3 percent, but given 2 patients with prolonged response the PFS was 5.4 months. mTOR inhibitors were the most successful in this cohort, with an ORR of 41% and a PFS of 9 months, with a subset of patients experiencing a response longer than 1 year (Sanfilippo et al., 2019). A subsequent case series found clinical benefit and disease control in a subset of patients with advanced malignant PEComas treated with antiestrogen therapy and mTOR inhibitors (Sanfilippo et al., 2020). A small subset of tumors were hormone receptor positive, but in this study these tumors showed no response to anti-estrogen alone. Once combined with Sirolimus (mTOR inhibitor), patients responded to the combined therapy with improvement in their disease burden, or at least maintained stable disease (Sanfilippo et al., 2020).

In conclusion, gynecologic PEComas are rare tumors. Prognosis is variable and related to certain histologic features. Symptoms can be nonspecific and preoperative diagnosis difficult, requiring morphologic and immunohistochemical review by a pathologist. Determining a treatment plan should be a multi-disciplinary effort. The rarity of the disease and resultant lack of established treatment guidelines highlight the need for improved awareness of this diagnosis and more clinical data.

CRediT authorship contribution statement

Annelise M. Wilhite: Conceptualization, Writing – review & editing. **Valeria Dal Zotto:** Writing – review & editing. **Paige Pettus:** Writing – original draft. **Julie Jeansonne:** Writing – original draft. **Jennifer Scalici:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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