1   A novel *SERPINE1-FOSB* fusion gene in a case of pseudomyogenic

2   hemangioendothelioma results in activation of intact FOSB and the

3   PI3K-AKT-mTOR signaling pathway and responsiveness to sirolimus

4   Abbreviated title: A novel *SERPINE1-FOSB* fusion gene in PHE

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22

23 **Abstract**

24 Pseudomyogenic hemangioendothelioma (PHE) is an extremely rare disease that

25 affects mainly the young and more men than women. PHE are multicentric, locally

26 aggressive, have low metastatic potential, and affect multiple tissue planes. Genetic

27 aberrations are frequently detected in PHE and may play important roles in the

28 occurrence, development, and treatment of this disease. In this study, we report a case

29 of PHE with a novel *SERPINE1-FOSB* fusion gene. The fusion introduced a strong

30 promoter near the coding region of *FOSB*, resulting in overexpression of intact FOSB.

31 Immunohistochemical analysis showed overexpression of pAKT and mTOR in tumor

32 cells, suggesting activation of the PI3K-AKT-mTOR signaling pathway. The patient

33 responded well to targeted therapy with sirolimus, an mTOR inhibitor. Our study

34 correlated dysregulation of a specific signaling pathway and the effectiveness of a

35 targeted therapy to a specific genetic aberration. This information may be useful for

36 future investigations of targeted therapeutics and provide a potential predictive

37 biomarker for therapeutic effectiveness in cases of PHE with this genetic aberration.

38

42

Introduction

43

44 Pseudomyogenic hemangioendothelioma (PHE) is an extremely rare disease that was

45 included in the 2013 WHO classification of soft tissue and bone tumors.[1] This disease

46 occurs mainly in the young population and affects more men than women. PHE are

47 typically multicentric, locally aggressive, have low metastatic potential, and affect

48 multiple tissue planes. [1, 2]

49 Histologically, PHE is characterized by loose fascicles of spindled and epithelioid

50 cells, abundant eosinophilic cytoplasm, and vesicular nuclei with distinct nucleoli. In

51 some cases, neutrophilic inflammatory infiltrates have been noted.[1, 2]

52 Immunohistochemically, tumor cells are positive for factor VIII, FLI-1, INI-1,

53 vimentin, MDM2, CDK4, CD31, cytokeratin AE1/AE3, EMA, and P63 and negative

54 for CD34, S-100, SMA, desmin, MyoD1, and HMB45.[2, 3] Genetically, chromosomal

55 rearrangements that result in the fusion of all or part of the *FOSB* coding region with

56 the promoters of other genes, such as *SERPINE1*, *ACTB*, *WWTR1*, and *CLTC*, have

57 been frequently identified in PHE, suggesting that activation of *FOSB* plays an

58 important role in the pathogenesis.[2, 4-11]

59 In terms of PHE treatment, the multifocal nature and high risk of relapse limit the

60 efficacy of surgical excision.[3, 12] Conventional chemotherapy has been administered in

61 some cases, with variable efficacy. However, intolerable toxic effects have been

62 noted.[12] In contrast, several targeted drugs, such as sirolimus, everolimus, and

63 telatinib, have shown efficacy with fewer side effects than chemotherapy.[12-16]

64 Unfortunately, the low incidence of PHE does not allow investigators to perform

65   systematic clinical trials to evaluate the efficacy of a specific treatment, and long-term

66   follow-up data for a specific treatment are limited. Therefore, no systemic therapies

67   have been officially approved for the management of PHE. Thus, in depth knowledge

68   regarding the pathogenesis and treatment and follow-up data for each case of PHE are

69   valuable for understanding and managing this rare disease.

70   Here, we report the diagnosis, genetic examination, treatment, and follow-up of a

71   patient with PHE and discuss the correlation of genetic aberrations with signaling

72   pathway dysregulation and therapeutic effectiveness.

73   **Materials and methods**

74   **Histological and immunohistochemical analysis**

75   Resected tumor samples were fixed in 10% buffered formalin and embedded in

76   paraffin to prepare 4-mm sections. For histological analysis, the sections were stained

77   with hematoxylin and eosin. Immunohistochemical analysis of cytokeratin AE1/AE3,

78   CD31, ERG, INI-1, BCL-2, Ki67, CD34, D2-40, S-100, SMA, and STAT6 was

79   performed using the BenchMark XT automated slide preparation system (Roche).

80   Immunohistochemical analysis of FOSB, pAKT, and mTOR was performed as

81   follows. The paraffin was removed from the sectioned tumor samples with xylene,

82   and the sections were rehydrated in a graded series of ethanol, followed by

83   heat-induced epitope retrieval in a pressure cooker and blocking of endogenous

84   peroxidase activity. Next, the sections were incubated with primary antibodies

85   overnight at 4 °C and then with a rabbit secondary antibody and finally reacted with 3,

86   3′-diaminobenzidine. The samples were counterstained with hematoxylin. Finally, the

87   slides were analyzed using an E200MV microscope (Nikon).

88   **Detection of the *SERPINE1-FOSB* fusion gene**

89   RNA was extracted from a freshly resected tumor sample using the RNeasy Mini Kit

90   (Qiagen) and reverse transcribed using the RevertAid First Strand cDNA Synthesis

91   Kit (Thermo Fisher) according to the manufacturer's protocol. The cDNA was

92   amplified in a 20-µL reaction containing $1\times$ FastPfu Buffer (TransGen Biotech,

93   Beijing, China), 1 U of TransStart® FastPfu DNA polymerase (TransGen Biotech),

94   2.5 mmol/L Mg^{2+}, 0.2 mmol/L of each deoxy-nucleoside triphosphate, and 0.2 µmol/L

95   each forward and reverse primer. Based on a previous study,[4] an upstream primer

96   targeting *SERPINE1* (5′-AGAGCGCTGTCAAGAAGACC-3′) and a downstream

97   primer targeting *FOSB* (5′-GTTCCCGGCATGTCGTAG-3′) were used. PCR was

98   performed on a ProFlex PCR System (Thermo Fisher) under the following cycling

99   conditions: 95 °C for 3 min, followed by 30 cycles at 95 °C for 30 s, 58 °C for 30 s,

100   and 72 °C for 3 min, with a final extension for 5 min at 72 °C.

101   The PCR products were examined by electrophoresis on a 1% agarose gel containing

102   $1\times$ GoldView^{TM} Dye (SBSGENE, Shanghai, China) for staining. The recovered PCR

103   products were examined using commercial Sanger sequencing (Sangon, Shanghai,

104   China).

105   **Ethics statement**

106   Signed informed consent was obtained from the patient for the use of his materials

107   and publication of de-identified clinical data, including photographs. The study was

108   approved by the Research Ethics Committee of Zhongshan Hospital Xiamen

109   University.

110   **Results**

111   **Clinical diagnosis of the case**

112   A 61-year-old man with no specific history of disease presented with rapidly

113   progressive multifocal nodules and localized pain in the left hip and left iliac region

114   for more than 2 months. The skin lesions were discontinuous, raised, or subcutaneous,

115   0.3–1.5 cm in diameter, with a smooth surface (Fig. 1A). The physical examination

116   was otherwise normal, and superficial lymph nodes were not enlarged. Magnetic

117   resonance imaging (MRI) revealed multiple lesions in the ilium (Fig. 1C), gluteus

118   medius, gluteus mininus, and subcutaneous region of the left hip (Fig. 1H).

119   As shown in Fig. 2, histopathological examination of a biopsy sample from the left

120   hip revealed that the nodule was in the dermis and subcutaneous tissue and was

121   composed of loose fascicles of spindled and epithelioid cells, with abundant

122   eosinophilic cytoplasm and vesicular nuclei with distinct nucleoli. Neutrophil

123   infiltration and intravascular tumor thrombus were also observed.

124   Immunohistochemical analysis revealed that the biopsy was positive for cytokeratin

125   AE1/AE3, CD31, ERG, INI-1, BCL-2, and Ki67 (15%) (Fig. 3) and negative for

126   CD34, D2-40, S100, SMA, and STAT6 (data not shown).

127   Based on the clinical presentation, histomorphology, and expression of keratins and

128   endothelial markers in the immunohistochemical analysis, the nodules were diagnosed

129   as PHE.

130   **The tumor was responsive to sirolimus**

131   After diagnosis, the patient underwent surgical resection to remove the palpable

132   nodules and was administered two cycles of anlotinib hydrochloride (10 mg/d) every

133   2 weeks. During the first cycle of chemotherapy, fresh nodules developed, and pain

134   remained. During the second cycle of chemotherapy, no evidence of tumor

135   development was observed, and the pain was alleviated. However, no evident

136   improvement was noted on follow-up MRI, and chemotherapy was halted due to

137   drug-induced nosebleeds and periungual sclerosis (Fig. 1D and I). The patient was

138   then treated with radiotherapy 5 days a week (Monday–Friday) via 6 MV linear

139   accelerator at a dose of 5000 cGy. Unfortunately, no improvement was noted after 5

140   weeks of radiotherapy (Fig. 1E and J).

141   Eventually, targeted therapy with sirolimus, an orally available mTOR inhibitor, was

142   started (1 mg/day), and oxycodone (50 mg bid) was administered for pain control. At

143   2-month follow-up, no fresh nodules had developed, and the pain was alleviated (Fig.

144   1B). Moreover, no drug-induced toxic effects were noted on physical examination.

145   Therefore, the dose of sirolimus was increased to 2 mg/day. Follow-up MRI was

146   performed at 5 and 20 months after sirolimus treatment, which showed general

147   improvement of the disease (Fig. 1F, G, K and L), and the largest lesion in the left

148   gluteus medius had progressively shrunk. Since the pain was alleviated, a reduced

149   dose of oxycodone (10 mg each night) was sufficient for pain control. Based on the

150   clinical improvement and lack of side effects, sirolimus therapy and follow-up are

151   ongoing.

152   **The *SERPINE1-FOSB* fusion gene activates *FOSB* and the EGFR-pAKT-mTOR**

153   **pathway**

154   Since the nodules were diagnosed as PHE and they were responsive to sirolimus, we

155   investigated the possible pathogenetic and therapeutic mechanisms. We first examined

156   the nodules for the presence of a *SERPINE1-FOSB* fusion gene. As shown in Fig. 4A,

157   when the tumor DNA sample was amplified with primers designed for the presence of

158   a *SERPINE1-FOSB* fusion gene, an amplicon was generated. Sanger sequencing of

159   the amplicon revealed a novel *SERPINE1-FOSB* fusion gene, in which the

160   breakpoints of both genes were in non-coding exon 1. Moreover, a 52-bp fragment

161   from intron 1 of *SERPINE1* was inserted at the fusion junction (Fig. 4B). Since the

162   coding region of *FOSB* was unaffected, the fusion gene could generate an intact

163   FOSB protein. Next, we examined the expression levels of FOSB, pAKT, and mTOR

164   in the tumor. As shown in Fig. 3, strong expression was noted for these targets,

165   suggesting that the fusion gene activates FOSB and the PI3K-AKT-mTOR signaling

166   pathway.

167   **Discussion**

168   Genetic aberrations play important roles in the occurrence, development, and

169   treatment of various human tumors. In PHE, chromosomal rearrangements leading to

170   the fusion of *FOSB* (the whole or partial coding region) with other genes, such as

171   *SERPINE1*, *ACTB*, *WWTR1*, and *CLTC*, have been identified.[2, 4-11] The common

172   feature of these cases is that the fusion introduces a strong promoter, resulting in

173   deregulated overexpression of intact, partial, or chimeric FOSB. However, the

174   pathogenic mechanism by which these genetic aberrations lead to PHE, which is of

175   value for the development of effective targeted treatments, remains largely unknown.

176   Recently, van IJzendoorn et al.[16] demonstrated that a *SERPINE1-FOSB*

177   fusion-derived chimeric protein could function as an active transcription factor that

178   was not only capable of regulating its own transcription but also upregulating the

179   expression of PDGFRA and FLT1. In their case, the tumors were responsive to

180   telatinib, a drug currently in clinical trials, that can block self-regulation of the fusion

181   gene by specifically affecting PDGFRA, FLT1, and FLT4 signaling and

182   downregulating SERPINE1. However, the presence of different genetic aberrations,

183   such as fusions with different genes or different domains, could alter the pathogenesis

184   as well as the treatment. Therefore, further investigation is required to demonstrate

185   whether this drug is effective in cases with other genetic aberrations such as

186   *SERPINE1-FOSB* fusions with intact or truncated *FOSB* or *ACTB-FOSB* fusions.

187   Similar to a previous case,[15] in our case, mTOR was overexpressed as was pAKT (Fig.

188   3), suggesting activation of the PI3K-AKT-mTOR signaling pathway, one of the most

189   frequently dysregulated pathways in human cancers that regulates important cellular

190   functions, including metabolism, motility, growth, and proliferation.[17] Dysregulation

191   of this pathway supports the survival, expansion, and dissemination of cancer cells.[17]

192   Genetic alterations in specific oncogenes or tumor suppressor genes, such as *PIK3CA*,

193   *PIK3R1*, *AKT*, *MTOR*, *TSC1*, and *TSC2*, can aberrantly activate this pathway via

194   diverse mechanisms. However, these genetic alterations also provide opportunities for

195   therapeutic targeting of this pathway and potential predictive biomarkers of

196   therapeutic effectiveness.[17] Currently, several distinct classes of drugs targeting the

197   PI3K-AKT-mTOR signaling pathway, including PI3K and AKT inhibitors, as well as

198   mTOR inhibitors, have been developed and have shown clinical potential.[18] mTOR

199   inhibitors, such as sirolimus and everolimus, have been effectively used for targeted

200   therapy of PHE.[12-15] However, the genetic information for mTOR inhibitor-responsive

201   cases is limited. In some cases, the genetic information was missing,[14] while in others,

202   although a translocation or gene fusion was reported, the translational products of the

203   fusion gene were not described.[13, 15] Most recently, Bridge et al.[7] reported a

204   *CLTC-FOSB* fusion gene resulting in a chimeric protein in a case of PHE, and the

205   tumor was responsive to sirolimus therapy. In our study, we clearly correlated the

206   effectiveness of sirolimus therapy with a PHE-related genetic aberration, that is, a

207   *SERPINE1-FOSB* fusion resulting in overexpression of intact FOSB. This genetic

208   aberration could be a predictive biomarker for effective sirolimus therapy. FOSB

209   belongs to the Fos family, which is associated with various cellular functions,

210   including proliferation, differentiation, and transformation, and it is frequently

211   involved in the pathogenesis of vascular tumors.[19-22] However, the causal relationship

212   between FOSB overexpression and activation of the PI3K-AKT-mTOR signaling

213   pathway remains unclear. Nonetheless, the use of combinations of inhibitors targeting

214   the PI3K-AKT-mTOR signaling pathway in PHE cases is worthwhile, since this

215   strategy has been shown to be more effective than monotherapy, owing to the

216   inhibition of compensatory mechanisms involved in intrinsic and adaptive

217   resistance.[23, 24] Future investigations of the interconnecting cascades between the

218   PHE-related genetic aberrations and this signaling pathway will advance our

219   knowledge of PHE and aid in the development of personalized agents with greater

220   target specificity and optimal therapeutic index.

221   In conclusion, we report a novel *SERPINE1-FOSB* fusion gene in a patient with PHE

222   that was responsive to sirolimus therapy. The fusion gene resulted in overexpression

223   of intact FOSB, pAKT, and mTOR, suggesting activation of the PI3K-AKT-mTOR

224   signaling pathway. Our study correlated the dysregulation of a specific signaling

225   pathway and the effectiveness of a specific targeted therapy to a specific genetic

226   aberration, which could promote the investigation of therapeutic targets and provide a

227   predictive biomarker of therapeutic effectiveness for PHE with this type of genetic

228   aberration.

229   **Acknowledgments**

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303

304 **Figure 1. Skin lesions and magnetic resonance imaging of the case.** (A) Multiple

305 nodules were present at diagnosis. (B) Remission of the lesions was evident after

306 sirolimus therapy for 2 months. Lesions with high signal intensity in the ilium at

307 diagnosis (C), after chemotherapy (D), after radiotherapy (E), and after sirolimus

308 therapy for 5 (F) and 20 months (G), respectively. Lesions with high signal intensity

309 in the gluteus medius, gluteus mininus, and subcutaneous region of the left hip at

310 diagnosis (H), after chemotherapy (I), after radiotherapy (J), and after sirolimus

311 therapy for 5 (K) and 20 months (L), respectively. The size of the largest lesion was

312 indicated.

313

314

315 **Figure 2. Histopathological examination of a biopsy sample from the left hip.**

316

317 **Figure 3. Positive immunohistochemical staining of a biopsy sample from the left**

318 **hip (400×).**

319

320   **Figure 4. Identification of a *SERPINE1-FOSB* fusion gene.** (A) Amplification of

321   the fusion gene with a specific primer pair. (B) Sanger sequencing of the amplicon

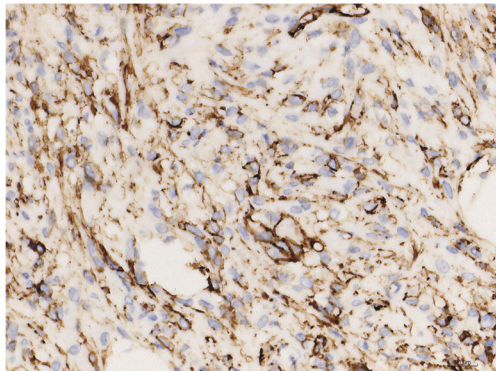322   showing the structure of the fusion gene. NTC: no template control.
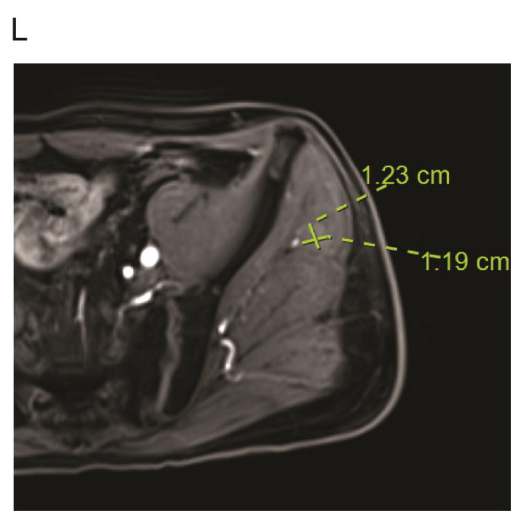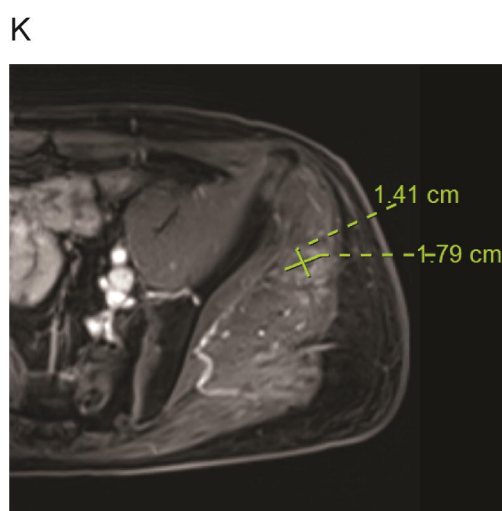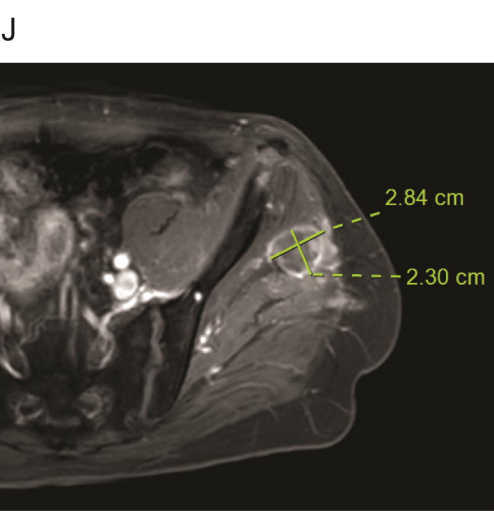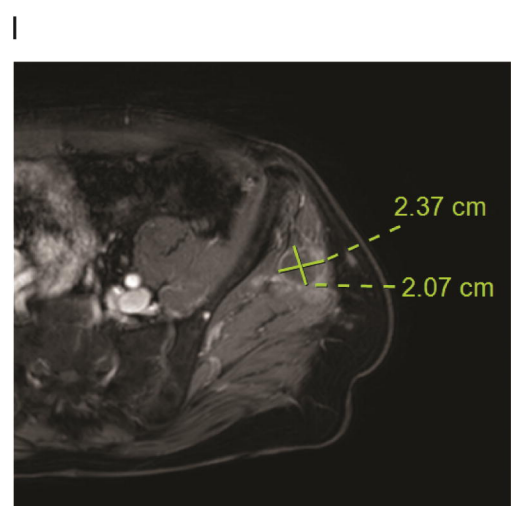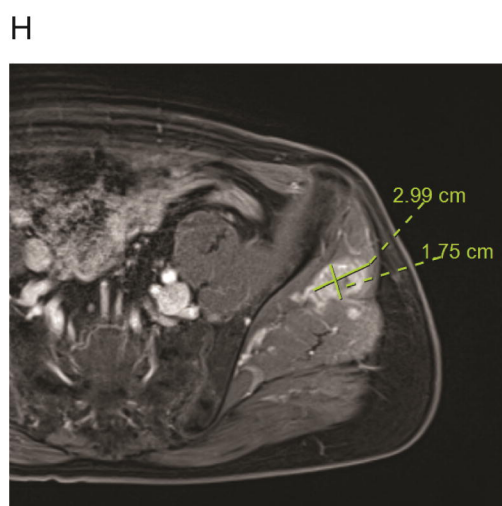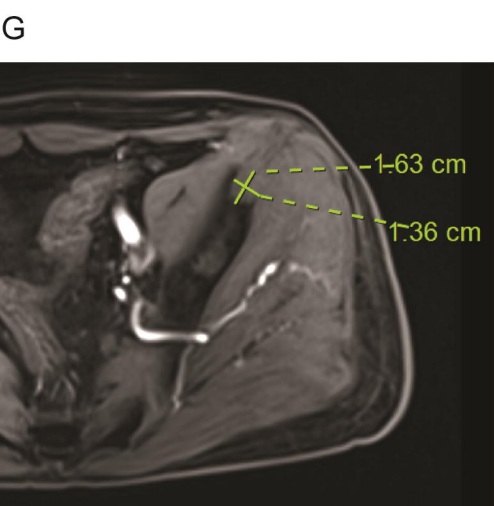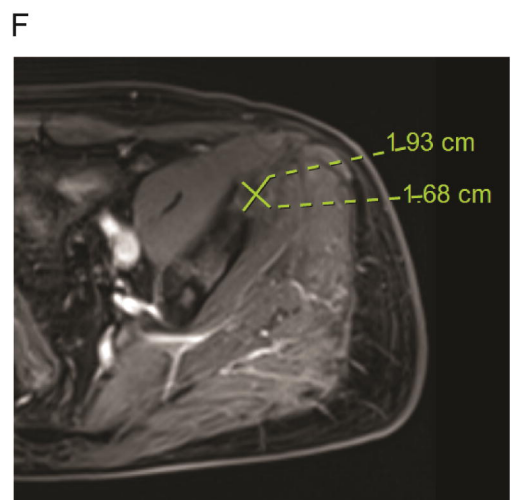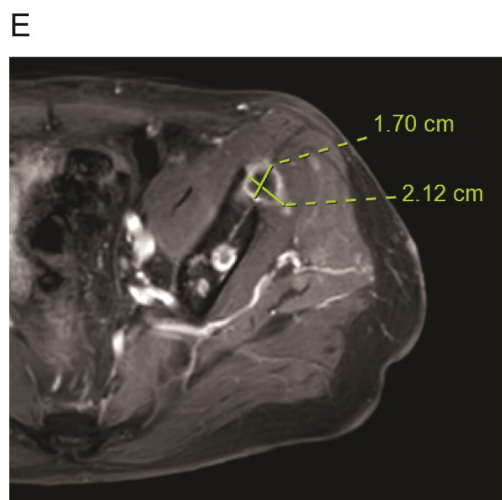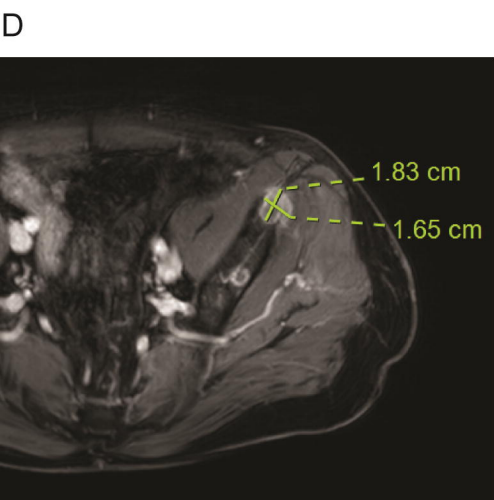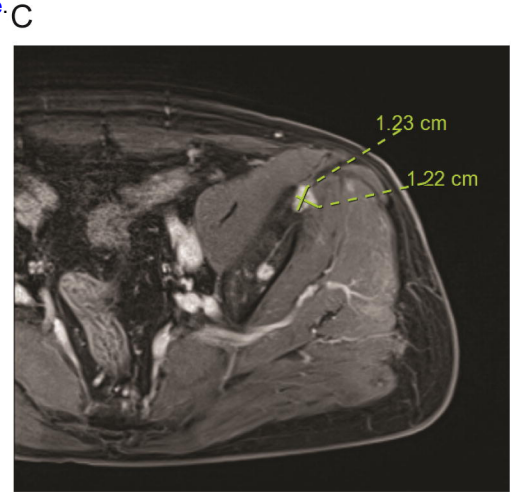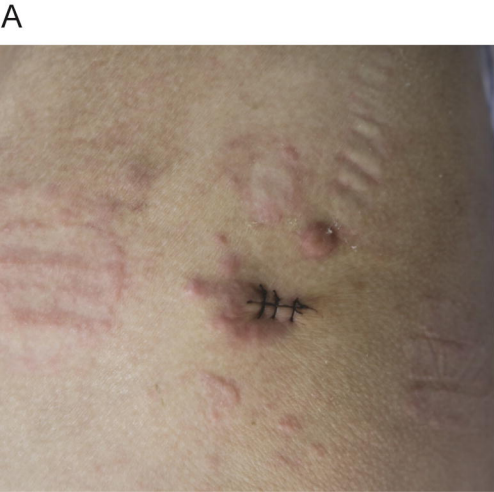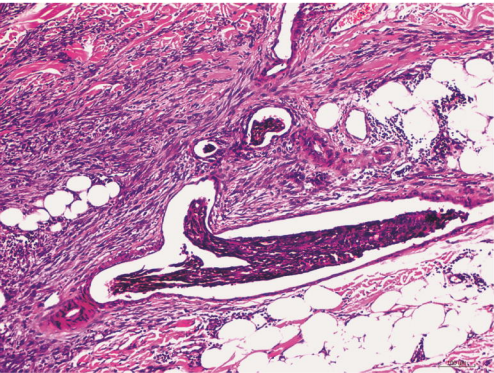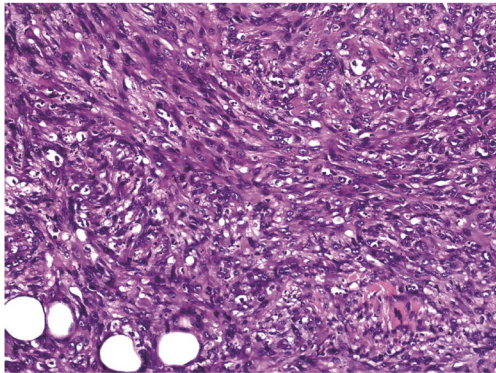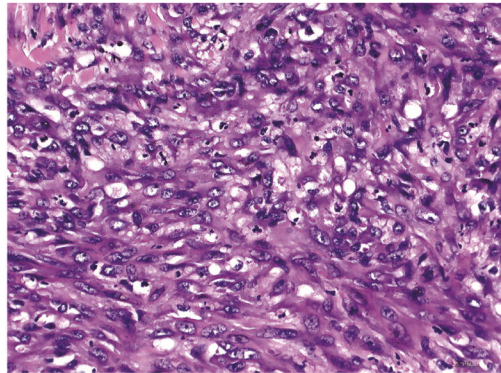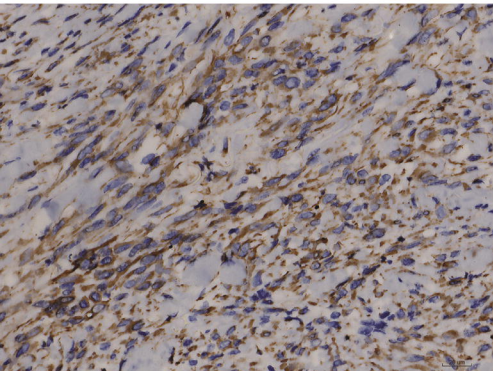
| 100 × | 200 × | 400 × |

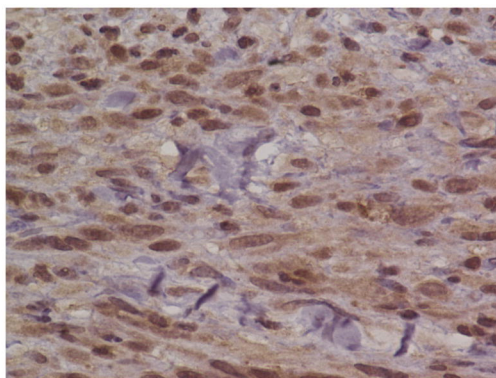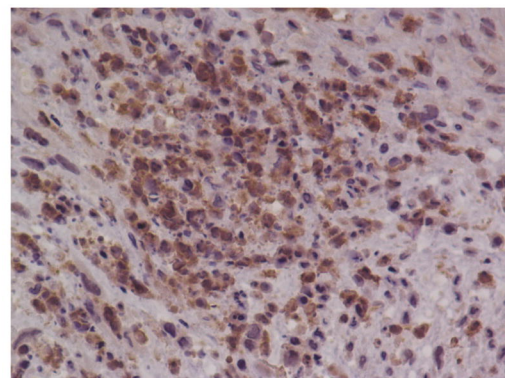| AE1/AE3	CD31	ERG
INI-1	BCL-2	Ki67
FOSB	pAKT	mTOR
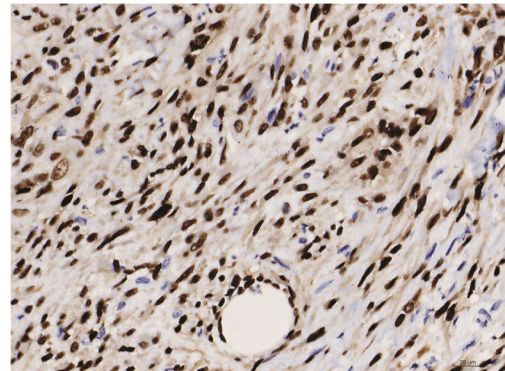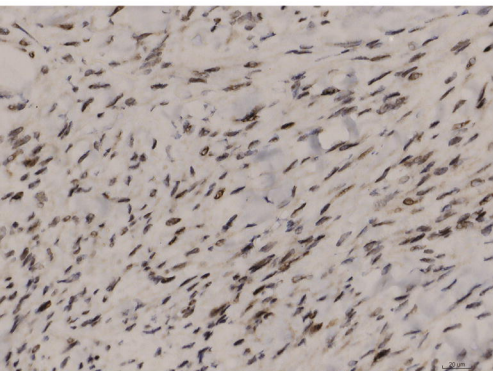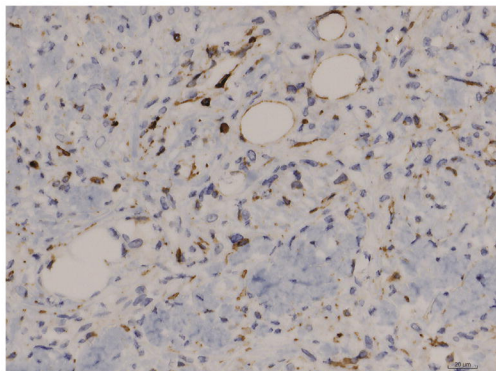
A
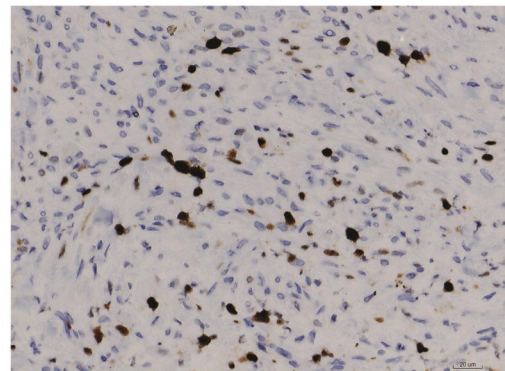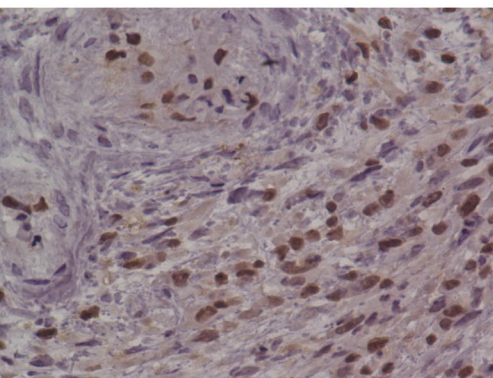
B

SERPINE1 exon 1
(-157, NG_013213.1)

SERPINE1 intron 1
(1010-1061, NG_013213.1)

FOSB exon 1
(5406 - , NG_029675.1)