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Gastrointestinal stromal tumor of the pancreas: a case report and review of the literature

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Summary. Gastrointestinal stromal tumours (GIST) represent a rare borderline neoplastic disease, which is currently thought to arise from the interstitial cells of Cajal, very few cases of pancreatic GIST having been reported so far. We report a case of a 60 year-old man with an incidental imaging (MRI) finding of a solid mass in the pancreatic head, which histological examination revealed to be a GIST. The patient had a disease recurrence after 42 months, received systemic treatment with Imatinib with benefit, and is still alive 53 months after diagnosis with a good quality of life. Although the studies published on pancreatic GIST are rare, we agree with most authors that GIST should always be considered in the differential diagnosis of a solid pancreatic mass, and a preoperative histological diagnosis possibly supported by intraoperative histological confirmation may be remarkably useful in order to tailor the surgical approach. Finally, despite its high risk, pancreatic GIST does not imply a poor prognosis if correctly treated by loco-regional surgical excision: its course depends on handling any complications of major abdominal surgery, which may be very serious in the case of the pancreatic localization.

Key words: gastrointestinal stromal tumours, pancreas, humans, review

«Tumore stromale gastrointestinale del pancreas: caso clinico e revisione della letteratura»
Riassunto. I tumori stromali gastrointestinali (GIST) rappresentano una rara patologia neoplastica dal comportamento biologico borderline, che comunemente si considera originata dalle cellule interstiziali di Cajal. Dal momento che sono stati segnalati ad oggi solo pochissimi casi di GIST pancreatico, riportiamo il caso di un uomo di 60 anni con una diagnosi incidentale all'imaging (MRI) di una massa cefalopancreatica solida, che all'esame istologico è risultata essere un GIST. Il paziente ha avuto una recidiva di malattia dopo 42 mesi, ha ricevuto una terapia sistemica con Imatinib con beneficio, ed è ancora vivo 53 mesi dopo la diagnosi con una buona qualità di vita. Anche se gli studi pubblicati sui GIST pancreatico sono rari, concordiamo con la maggior parte degli autori nel sostenere che il GIST debba sempre essere preso in considerazione nella diagnosi differenziale di una massa pancreatica solida, e che una diagnosi istologica preoperatoria, eventualmente supportata da una conferma istologica intraoperatoria, possa essere di grande aiuto nella scelta dell'approccio chirurgico più opportuno. Infine, nonostante l'alto rischio, il GIST pancreatico non risulta generalmente associato ad una prognosi sfavorevole. Tuttavia, bisogna adottare particolare cautela durante l'intervento chirurgico per prevenire eventuali complicanze legate alla chirurgia addominale maggiore, che nel caso della localizzazione pancreatica possono essere anche molto gravi.

Parole chiave: tumori stromali gastrointestinali, pancreas, uomo, revisione della letteratura

Abbreviation list
GIST: Gastrointestinal stromal tumour;
CT: computer tomography;
EGIST: extra-gastrointestinal stromal tumour;
FDG-PET-CT: positron emission tomography-computed tomography with fluorodeoxyglucose;
PDGFRA: platelet-derived growth factor receptor-alpha.

Introduction

Gastrointestinal stromal tumours (GIST) are a rare borderline neoplastic disease, which is currently thought to arise from the interstitial cells of Cajal (1-4). The most common anatomical site of occurrence is the stomach, followed by the small bowel and colon (5). However, the literature does describe few cases originating outside the gastrointestinal system, so-called EGISTs (extra-gastrointestinal stromal tumours).

The first case of pancreatic GIST was reported in 2004 (6), and only a few cases in all have been reported so far (7-17). The histological origin remains a subject for debate. Although some observations suggest that EGISTs are more likely to be mural GISTs with extensive extramural growth and loss of contact with the muscle layer of the gut (1, 14), other studies confirm the possibility that GIST can involve the pancreas as a primary site (13).

In this paper, we describe the case of a patient suffering from pancreatic GIST with a significantly long follow-up and a favourable prognosis. We also review the literature in order to clarify some aspects of diagnosis, treatment and prognosis of this rare pathology.

Materials and methods

We present a case report of pancreas GIST diagnosed in 2008 with more than 3 years follow-up and managed with surgery and medical treatments. Follow-up was regularly performed by radiological imaging as part of clinical examination.

We also performed a review of the published literature. We searched for all articles written in English between 2000 and 2012 on Medline, focusing our research on the following keywords: gastrointestinal stromal tumor, GIST, pancreatic, and pancreas. We considered all articles dealing with management and outcome of pancreatic GIST and three reviewers independently extracted data onto a standard form. The data abstracted related to predetermined variables (patient characteristics, symptoms, tumour location, tumour characteristics, treatment, follow-up and outcome). Geographic locations, site of treatment, and time frame for cancer diagnosis were recorded, in order to avoid any possible population overlap; when these features suggested a population overlap between two reports, the article with the longer follow-up, larger data set, or more detailed information was used, while the other was excluded from analysis. Any discrepancies among the three reviewers were addressed by a joint re-evaluation of the original article. We considered for inclusion all case reports, case series, and observational studies that evaluated management and outcome in pancreatic GIST patients. All relevant studies proved to be case reports because of the rarity of this disease and because the first publication on pancreatic GIST was in 2004. In this systematic review of the literature we included only articles written in English on human subjects with the full text available for data retrieval. Specific exclusion criteria were: studies considering GIST from other origins (e.g. bowel, stomach, etc.), or studies on non-human subjects, and articles not written in English. We also excluded reviews, letters to the editor without original data, and editorials. Conference abstracts were likewise excluded due to lack of details regarding management and outcome.

Statistical analysis was performed by R (version 2.15.0), considering $p<0.05$ as significant. We presented data as means (± standard deviation), or medians (with interquartile range - IQR) or prevalence values. A 95% confidence interval was presented when appropriate. A cumulative events curve was also drawn to show recurrences during the course of follow-up.

Case presentation

A 60 year-old man was referred to our Surgical Outpatients in April 2008 for the incidental ultrasonographic finding of a voluminous mass in the right

upper-mesocolic abdominal region. The biochemical laboratory findings revealed only an increase in the phlogistic indexes and a minimal increase in gamma-glutamiltransferase and alcalin phosphatase, while tumour markers were negative. The pathological anamnesis included a microadenoma of the hypophysis operated on in 2005, arterious hypertension, diabetes mellitus type 2 and a history of previous peptic ulcer.

The ensuing CT scan described a 12-cm non-homogeneous lesion with irregular margins and a wide central hypodense necrotic area (Figure 1A). This mass seemed to originate from the pancreatic head, to be not cleavable from the principal adjacent vasculo-nervous structures, and to partially occlude the inferior vena cava pressing its walls but without infiltrating it.

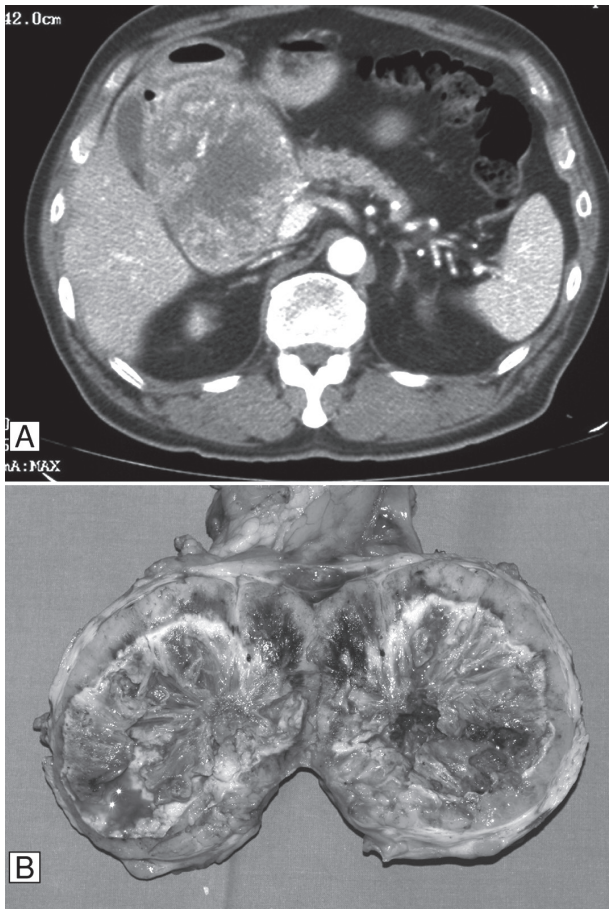

Figure 1. Panel A: CT scan revealed a 12-cm-sized, solid, non-homogeneous lesion with irregular margins and a wide, central, hypodense, necrotic area. The lesion seems to be part of the pancreatic head and presses the duodenum. Panel B: Macroscopic aspect of the surgical specimen.

The CT scan excluded any loco-regional lymph node involvement.

Oesophago-gastro-duodenoscopy detected a small ulcer of the duodenal bulbus, which was biopsied together with the suspicious pancreatic lesion, and both histological findings described a GIST.

The patient was then operated and, other organ involvement being ruled out, the lesion was removed by duodeno-cephalo-pancreasectomy (Whipple procedure). Macroscopically, the lesion presented as a multinodular mass with a central haemorrhagic necrosis, separate from the duodenal wall, which incorporated and occluded the intrapancreatic biliary duct (Figure 1B).

Microscope examinations confirmed a mesenchymal neoplasia, 2 mytosis/50 HPF, with focal areas of leyomuscular differentiation, and neoplastic spindle cells arranged in sheets and fascicles, with necrotic areas. The tumour mass proved well separated from the pancreatic parenchyma by a fibrous pseudocapsule (Figures 2A and 2B). Immunohistochemical analysis showed strong positivity for CD117/KIT expression in the neoplastic cells (Figure 2C). Surgical resection margins and peripancreatic lymph nodes proved negative for neoplastic infiltration.

The patient was discharged on the twelfth post-operative day in good health and without any surgical complications. He then underwent frequent regular clinical and instrumental follow-ups, including FDG-PET-CT at 4 months and then yearly, a chest-abdominal CT scan at 6 months and then yearly, and an abdominal ultrasound at 9 months, which proved negative for disease persistence or recurrence.

After 42 months of follow-up, FGD-PET-CT detected a hepatic hypercaptation arousing suspicion of recurrence. Consequently, the oncologist proposed systemic treatment with Imatinib mesylate. Subsequent FDG-PET-CT controls demonstrated a reduction in the metabolic activity of the suspicious area, suggesting a complete response to the hepatic recurrence.

Finally, 54 months after e diagnosis the patient is alive, without any evidence of disease, and with good quality of life.

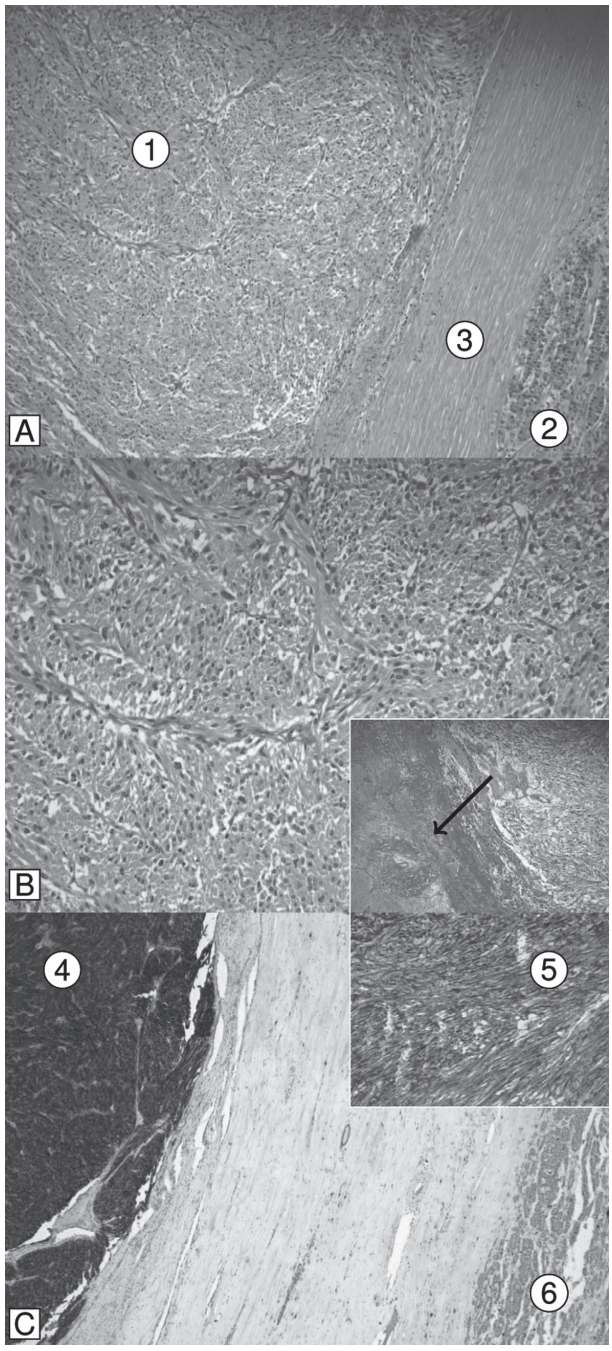

Figure 2. Panel A: tumor mass (1) is separated by pancreatic parenchyma (2) by a fibrous pseudocapsule (3) (H&E, Original Magnification, 100x). Panel B: Neoplastic spindle cells are arranged in sheets and fascicles patterns (H&E, Original Magnification, 200x) with necrotic areas (insert arrow). Panel C: Immunohistochemical analysis shows strong CD117/KIT-positivity in the neoplastic cells (4), upper left, Original Magnification 50x, and (5), insert, Original Magnification 400x) (CD117, 9.7 clone, Haematoxylin counterstain). On the bottom right, (6) normal pancreatic parenchyma.

Literature review

In Tables 1 and 2 and Figure 3 and 4 we present data from our systematic review.

Discussion

This case concerns a rare localization of GIST; in the literature pancreatic GIST has previously been reported in no more than twelve papers (6-17). We collected data on all previous reported cases of pancreatic GIST (Table 1) and compared them with our own, in order to clarify some aspects of diagnosis, treatment and prognosis of this rare disease.

The mean age at presentation proved to be 56.08 years (±13.29) and 53.8% were female patients. In 46.2% of cases the diagnosis was incidental through imaging performed for other problems, while in the other 50% or so of cases the main symptoms were abdominal pain especially located in the epigastrium, asthenia, nausea, and vomiting (Table 2). The most frequent location of pancreatic GIST proves to be the head (50%), but in all cases there is compression of the pancreatic tissue and the pancreatic vascularisation identifies the site of origin. In our case, there was also a local infiltration of the duodenal wall which may have compromised the correct preoperative localization of the primary tumour.

The mean lesion size proved to be 10.42 cm (±5.35) and the mitotic count was lower than 15/50HPF in 81.8% of cases. Despite the generally low mitotic count, the majority of pancreatic GISTs can be considered at high risk due to the macroscopic size of specimens, and this may be related to the delayed diagnosis in the absence of symptoms. Moreover, Trabelsi and colleagues have suggested that GISTs with a primary pancreatic localization are usually at high risk of malignancy (13), and indeed our single case was defined by the pathologist as high risk due to some microscopic aggressive features. According with the literature, lesion size and mitotic count may have an important role as outcome predictors (18), and in fact among the considered cases, high risk pancreatic GISTs were more likely to develop recurrences.

Immunohistochemistry detected CD117/KIT positivity in 83.33% of cases and CD34 positivity in

Table 1.- Review of the literature about pancreatic GIST.

Authors and year of publication	Age (ys)	Gender	Symptoms	Localization	Size (cm)	Mytosis number	Risk	Immunohistochemistry	Margins	Postoperative complications	Adjuvant therapy	Outcome	Follow up (months)
Neto et al. 2004	67	F	epigastralgia, and weight loss	body	20	120/50HPF	high	CD117+ CD34+ CK7- CK20- desmin-sinaptophysin	NA	NA	yes	hepatic and retroperitoneal recurrence	1
Yamaura et al. 2004	54	F	none	tail	14	low	high	CD34+ vimentin+ SMA- S100-	negative	none	NA	no evidence of disease	30
Krska et al. 2005	38	F	abdominal pain	body	17	1/50HPF	high	CD34+ CD117- vimentin+ SMA- S100- cromogranin-	NA	none	no	no evidence of disease	30
Daum et al. 2005	70	F	none	head	10	2/50HPF	high	CD117- CED34- S100- SMA- desmin- CK-	negative	yes	yes	no evidence of disease	6
Showalter et al. 2008	72	F	none	tail	7	3/50HPF	low	CD117+ S100- SMA-	NA	none	no	no evidence of disease	28
Yan et al. 2008	47	M	nausea and vomiting	head	2.4	low	low	CD117+ desmin-	NA	NA	NA	NA	NA
Herindhanavudhi et al. 2009	63	F	asthenia	body	16	5/50HPF	high	CD117+CD34+	NA	none	yes	NA	NA
Trabelsi et al. 2009	52	F	epigastralgia	head	10.5	NA	high	CD117+ CD34+ SMA - S100- CK- sinaptophysin-	negative	none	no	no evidence of disease	10
Goh et al. 2009	58	M	none	NA	9	NA	NA	CD117+	NA	NA	NA	NA	NA
Vij et al. 2011	35	M	asthenia and postprandial pain	head	6.5	15/50HPF	high	CD117+CD34- SMA- S100- CK- desmin-	negative	none	no	hepatic recurrence	24
Cecka et al. 2011	74	M	none	tail	11	5/50HPF	high	CD117+CD34+ SMA- S100-	NA	none	no	no evidence of disease	66
Soufi et al. 2012	39	M	epigastralgia	head	10	5/50HPF	high	CD117+CD34+	negative	none	yes	no evidence of disease	24
Uzzau et al. 2012	60	M	none	head	2	2/50HPF	high	CD117+CD34- SMA- S100-	negative	none	no	hepatic recurrence	42

Table 2. Cases description: patients characteristics, diagnosis, treatment, and outcome.

	Prevalence, * Mean (sd), ** Median (IQR)
Female gendre	53.8% (7/13)
Age (years)	56.08 (±13.29) *
Symptoms	
upper abdominal pain	23.1% (3/13)
diffuse abdominal pain	7.7% (1/13)
asthenia	15.4% (2/13)
nausea and vomiting	7.7% (1/13)
none	46.2% (6/13)
Localization	
head	50% (6/12)
body	25% (3/12)
tail	25% (3/12)
Mytosis.number >/=15/50HPF	18.18% (2/11)
Size (cm)	10.42 (±5.35) *
Risk	
high	75% (9/12)
low	25% (3/12)
Surgical margins negativity	100% (6/6)
Postoperative complications	10% (1/10) pancreatic fistula
Adjuvant therapy with Imatinib	50% (5/10)
Follow up (months)	26 (14-30) **
Outcome	
Hepatic (+/- retroperitoneal) recurrence	30% (3/10)
No evidence of disease	70% (7/10)

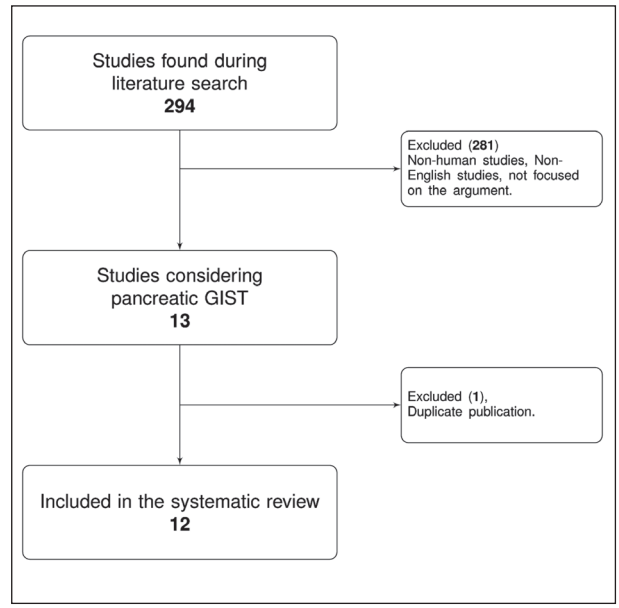

Figure 3. Flow chart of our systematic review.

70% of cases in which it was evaluated. Again, the literature confirms CD117/KIT as the most sensitive GIST marker, while different patterns emerge for CD34 and SMA in different parts of the gastrointestinal tract (19, 20). Moreover, an association of pancreatic GIST with CD117/KIT gene mutation has been demonstrated (10), as well as an association of EGISTs with mutations of PDGFRA (platelet-derived growth factor receptor-alpha) (21, 22).

Recently, some authors have reviewed the various inherited mutations associated with GIST syndromes, which have important clinical implications for the future understanding of this heterogeneous disease and the detection of new therapeutic targets (23). Furthermore, Papillon and colleagues described a case of malignant GIST in association with multiple endocrine neoplasia (MEN)-1 syndrome (24). And incidentally, even in the absence of any genetic investigation, one notes that our patient had previously been operated for a hypophysis adenoma.

Surgical strategy in cases of pancreatic GIST obviously depends on its location and size. Post-operative complications affected 10% of cases (pancreatic fistula), and are thus comparable with the complication rate of any major pancreatic surgery. Although a recent study demonstrates the predictive value of microscopic resection margins for disease-free survival (25), there were no data about margin involvement in the reports considered. In fact, resection margins proved negative for neoplastic infiltration wherever their status was described.

For high risk GISTs, the combination of surgery and Imatinib is highly indicated, and the literature suggests this combination may be of benefit in a neoadjuvant setting (26, 27). Among the pancreatic GISTs considered, adjuvant treatment with Imatinib was only performed in 50% of cases. The median follow up length was 26 months (IQR 14-30), with a favourable outcome in the majority of cases (70%) and the finding of hepatic metastasis in three patients (30%). Unfortunately, no data about overall survival emerge from the literature, and for what concerns disease-free survival we found that the recurrences rate is 10% at 1 year,

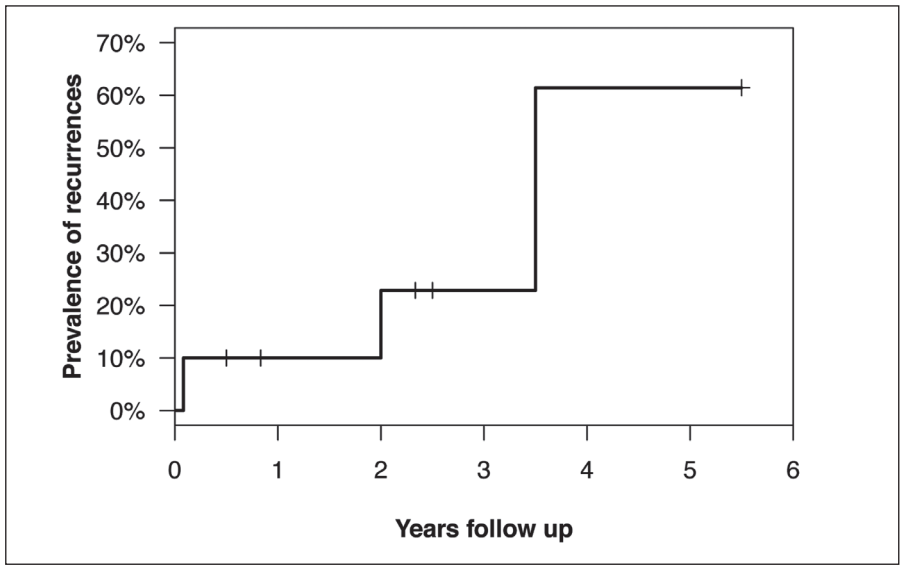

Figure 4. Prevalence of recurrences in the published literature.

25% at 3 years and 60% at 5 years (Figure 4). Consequently, the median follow-up is too short to allow any conclusion about the real recurrence incidence. Finally, in our opinion, the hepatic recurrence did not influence our patient's survival, probably due to his good response to Imatinib.

Conclusions

This case is interesting because of the significant length of the follow-up and the rarity of pancreatic origin GISTs in general. In fact, only twelve cases have been previously described in the literature, the majority with a very short follow-up. We agree with most authors that GISTs should always be considered in the differential diagnosis of solid pancreatic masses, and in our opinion a preoperative histological diagnosis if possible supported by intraoperative histological confirmation may be remarkably useful when it comes to tailor the surgical approach.

From our own data and the literature review, we can conclude that the pancreatic localization of GIST, despite its high risk, does not imply poor prognosis if correctly treated by loco-regional surgical excision. Its course depends on handling any complications of major, abdominal surgery, which may be very serious in the case of a pancreatic localization.

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