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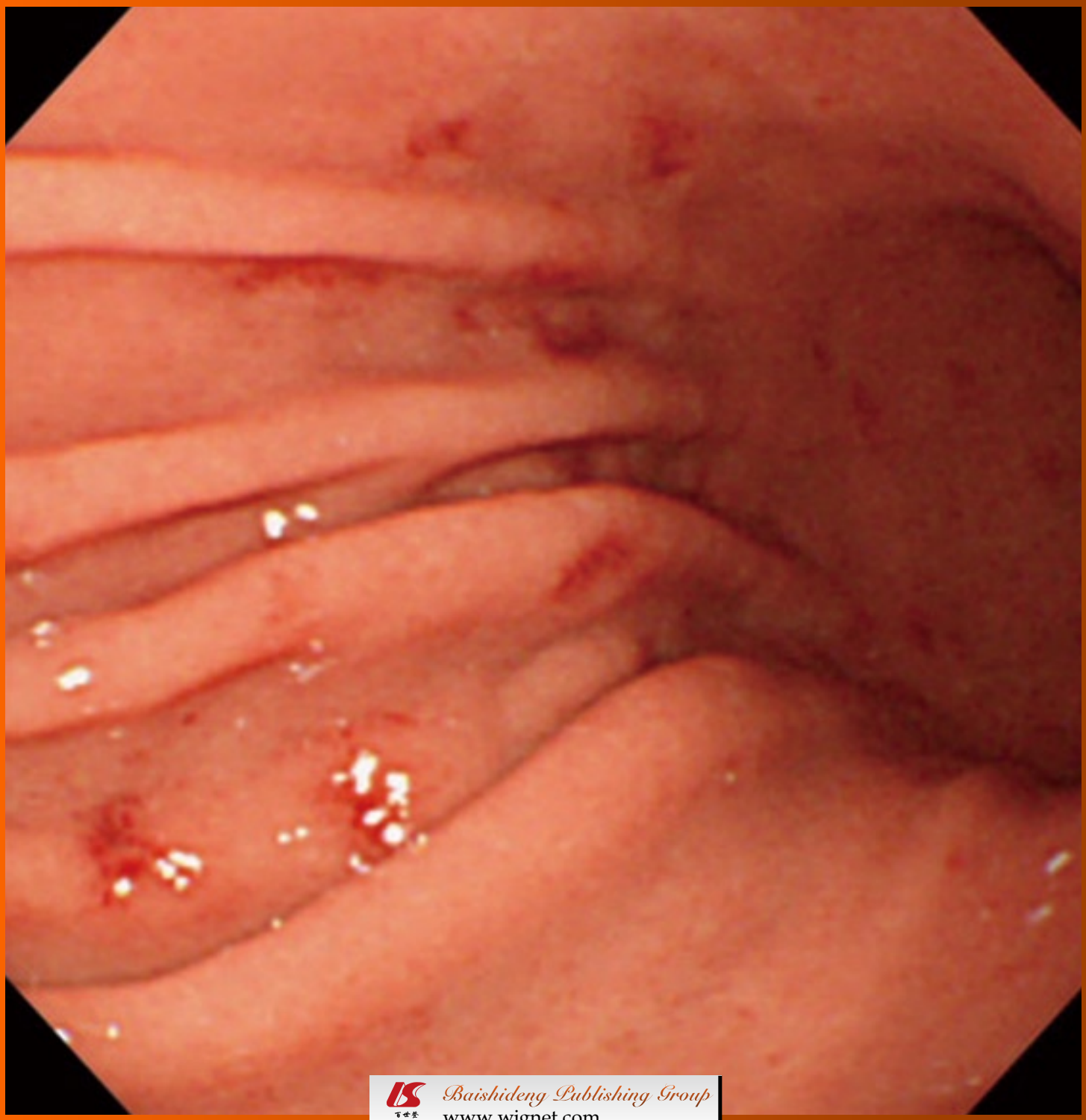

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EDITORIAL

Photodynamic therapy: Palliation and endoscopic technique in cholangiocarcinoma

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Abstract

Cholangiocarcinoma is the primary malignancy arising from the biliary epithelium. The disease is marked by jaundice, cholestasis, and cholangitis. Over 50 percent of patients present with advanced stage disease, precluding curative surgical resection as an option of treatment. Prognosis is poor, and survival has been limited even after biliary decompression. Palliative management has become the standard of care for unresectable disease and has evolved to include an endoscopic approach. Photodynamic therapy (PDT) consists of administration of a photosensitizer followed by local irradiation with laser therapy. Several studies conducted in Europe and the United States have shown a marked improvement in the symptoms of cholestasis, survival, and quality of life. This article summarizes the published experience regarding PDT for cholangiocarcinoma and the steps required to administer this therapy safely.

Key words: Cholangiocarcinoma; Cholestasis; Jaundice; Neoplasia; Palliation; Photodynamic therapy; Photofrin

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INTRODUCTION

Cholangiocarcinoma is the primary neoplasia originating from the biliary system. The incidence rate is 1-2 per 100000 people per year in the United States[1,2]. Initially thought to be an uncommon disease, the number of cases reported annually has been climbing[2-4]. Nearly two-thirds of cases of cholangiocarcinoma occur in patients between the ages of 50 and 70, and the tumor appears to have a male predominance[2,5]. Predisposing conditions include disorders such as primary sclerosing cholangitis, intrahepatic stones and choledocholithiasis, choledochal cysts, liver flukes, and previous exposure to the contrast agent thorium dioxide (Thorotrast)[6-16].

Complete surgical resection is the only treatment with potential for a cure. Unfortunately, more than 50% of patients present with unresectable disease at the time of diagnosis[17-19]. The prognosis at this stage is dismal, being approximately 3 mo without intervention, and 4-6 mo after palliative biliary decompression[20-25]. Even after curative (RO) resection the 5-year survival rate is only 30%-40%[26-28]. Successful palliation of biliary obstruction remains the main goal for reducing morbidity and mortality in these patients[21,29].

PALLIATION OF CHOLANGIOCARCINOMA

The approach to biliary decompression has evolved from a surgical approach, to percutaneous drainage, and finally to endoscopic management. Hepaticojejunostomy is associated with a 30-d postoperative mortality rate of

between 7% and 24%[30-34]. Furthermore, quality of life was only improved in a minority of patients undergoing surgery because of the time needed to recover[24,35,36]. Biliary stenting only provides temporary relief[37-42]. Adding chemotherapeutic agents has been largely unsuccessful; moreover, no standard chemotherapeutic regimen currently exists[43]. Various chemotherapeutic agents have been studied, with limited improvement in survival rates[44-46]. Radiotherapy is an area of great controversy regar ding its efficacy in cholangiocarcinoma, and is associated with an increased incidence of cholangitits, gastro-duode nitits, and longer hospitalization[47-49]. However, concurrent chemoradiotherapy with helical tomotherapy intensity modulated radiotherapy and capecatibine, in conjunction with photodynamic therapy, has been shown to be well tolerated in patients with hilar cholangiocarcinoma[50,51].

PRINCIPLE OF PHOTODYNAMIC THERAPY

PDT is a two step process. during which a photosensitizer is initially administered, followed by photoradiation[52]. Photofrin (porfimer sodium, Axcan Pharma Inc., Mont-Saint Hilaire, Canada) remains the most commonly used drug in this setting, since it has a selective nature and is preferentially retained by neoplastic tissue[53]. Laser ap plication at a specific wavelength starts the activation process by transforming the drug from its neutral ground state, into its activated state. In the presence of oxygen, cytotoxic singlet oxygen species are formed, destroying the dysplastic cells to which they are bound. These free radicals induce apoptosis and tumor necrosis to a depth of 4 mm to 6 mm[54,55]. Synergistically, nearby vascular channels are also affected, indirectly accelerating the process by cutting off the supply of vital nutrients.

PDT has been shown to reduce xenografted human cholangiocarcinoma tumor volume by 60% in a mouse model[56]. Recent reports and randomized controlled studies in which PDT was used as an adjuvant therapy, have shown a significant survival benefit in patients with unresectable cholangiocarcinoma, as well as a significant improvement in the quality of life after PDT and stenting[57,58].

TECHNIQUES

The technique used to execute the procedure has become standardized. PDT has typically been offered to pa tients with nonresectable cholangiocarcinoma, or as a neoadjuvant therapy. Staging can be performed with computed tomography and/or magnetic resonance imaging[58]. Resectability is usually defined according to the criteria of Vauthey and Blumgart[59].

Each patient found to be a candidate for PDT undergoes a thorough educational process. Indeed, specific education regarding sun exposure and protection is necessary in order to avoid severe sun-related phototoxicity, and should be provided to all patients prior to the procedure[58].

Endoscopic retrograde cholangiography (ERC) is per formed using therapeutic duodenoscope (TJF-140, TJF-160, and TJF-160VF; Olympus America, Center Valley, PA). After cannulation into the biliary tract, a cholangiogram is performed to help define the anatomic distribution of malignant tissue and the extent of disease within the biliary ducts. Careful opacification of the dilated segments is realized selectively. Bougie and balloon dilation of the stricture(s) to be treated is performed, to facilitate diffuser placement within the malignant stricture.

After placement of the diffuser probe within the stricture to be treated, photoactivation is performed at 630 nm with a light dose of 180 J/cm^2, fluence of 0.250 W/cm^2 and irradiation time of 750 s. One or more segments can be treated at the discretion of the endoscopist. When tumor length exceeds the maximal diffuser length, stepwise pull-back of the fiber under fluoroscopic guidance can be done. Placement of an endoprostheses is performed systematically after the photodynamic treatment to prevent cholangitis. Our group has recently demonstrated the safety and efficacy of choledochoscopy- guided PDT, allowing specific intraductal visualization of the stricture(s) to be treated[59].

For patients failing conventional ERC, a technique for photodynamic therapy using percutaneous biliary access can be used, in which a percutaneous drain is replaced with an 8French vascular sheath over a guidewire[60]. PDT is typically repeated at 3-mo intervals at which time all stents should be replaced. Stents are exchanged earlier in the case of premature occlusion or migration, to maintain optimal biliary drainage. All patients should receive perioperative antibiotic prophylaxis. Post-therapy, patients treated with PDT are advised to remain out of direct sunlight, since Porfimer sodium may cause prolonged photosensitivity lasting 30-90 d[61].

ACCESSORIES

Though other photosensitizers are now available, porfimer sodium is the most studied, and the only photosensitizer approved by the FDA. It is administered intravenously at a dose of 2 mg/kg body weight 48 h prior to illumination. A diode laser system (InGaAIP Laser Diode; Diomed Inc., Andover, MA) with a maximum power output of 2000 mW and a wavelength of 630 nm is used as a light source, delivered through a 3.0-m length fiber having a 2.5-cm-long cylindrical diffuser at its distal end (Pioneer Optics, Windsor Locks, CT). The diffuser can be inserted into a 10 F sheath of a plastic stent delivery system (MAJ-1419; Olympus America) and placed at the level of the stricture being treated. Alternatively, our group has been using the single operator choledochoscope (Spyglass, Boston Scientific, Natick, MA) as a platform to administer PDT[59].

RESULTS AND OUTCOMES

There have been several reports suggesting that PDT provides a survival benefit (Table 1)[52,58,61-66]. In 2003, Ort-

Table 1 Table comparing studies performed by using endoscopic retrograde cholangiopancreatography with photodynamic therapy with photofrin sodium for palliation of cholangiocarcinoma

Study	Year	*N*	Study type	Median TB before and after PDT	Mean PDT sessions (range)	Median survival (mo)	Adverse events phototoxicity, cholangitis *n* (%)
Ortner *et al*[62]	1998	9	Single Arm	18.6 > 6	1.5 (1-2)	14.6	1 (11), 0 (0)
Berr *et al*[62]	2000	23	Single Arm	11.2 > 1.1	3.0 (1-5)	11.1	3 (13), 8 (35)
Rumalia *et al*[63]	2001	6	Single Arm	2.7 > 1.3	2.3 (1-2)	> 6	2 (33), 2 (33)
Dumoulin *et al*[64]	2003	24	Single Arm	13.3 > 2.6	1-2	9.9	2 (8), 5 (21)
Ortner *et al*[52]	2003	20	Randomized	NA (decreased)	2.4 (1-5)	16.4	2 (10), 5 (25)
Ortner *et al*[52]	2003	31	Nonrandomized	11.8 > 3.1	1.5 (1-4)	14.2	3 (10), 6 (19)
Harewood *et al*[65]	2005	8	Single Arm	7.7 > 1.1	2.0 (1-5)	9.2	2 (25), 2 (25)
Witzigmann *et al*[66]	2006	68	Single Arm	NA (decreased)	2.0 (1-6)	12.0	8 (12), 38 (56)
Prasad *et al*[61]	2007	25	Single Arm	6.1 > 3.5	1.6 (1-4)	13.4	1 (4), 2 (8)
Kahaleh *et al*[58]	2008	19	Comparative	6.3 > 3.5	1.6 (1-3)	16.2	3 (16), 7 (37)

TB: total bilirubin; NA: not available; PDT: photodynamic therapy.

ner *et al*[52] conducted the first randomized controlled trial comparing survival rates in patients treated with biliary stenting alone with those treated with biliary decompression combined with photodynamic therapy. After 39 patients were enrolled in the study, improvement in survival and quality of life in the randomized PDT group was found to be so impressive [i.e. 493 d (n = 20) *vs* a median survival of 98 d (n = 19), $P < 0.0001$] that the trial was terminated prematurely. However, only patients failing conventional ERC were enrolled in that trial, making a repeat ERC indispensable, which might account for the benefit attributed to PDT.

In 2007, the Mayo team demonstrated that patients with unresectable cholangiocarcinoma without a visible mass benefited from early treatment with PDT[61]. In 2008, our group published findings comparing stenting alone with a combination therapy of stenting and photodynamic therapy[58]. Kaplan-Meier analysis demonstrated improved survival in the PDT group compared with the stent-alone group (16.2 *vs* 7.4 mo, $P < 0.004$). Mortality in the PDT group at 3, 6, and 12 mo was 0%, 16%, and 56% respectively. The corresponding mortality in the stent group was 28%, 52%, and 82% respectively. The difference between the two groups was statistically significant at 3 and 6 mo, but not at 12 mo. Although it was not entirely clear whether the benefit was directly related to PDT or the number of endoscopic retrograde cholangiopancreatography sessions, this study helped to strengthen the findings published by Ortner *et al*[52] in 2003. Furthermore, adverse effects in the PDT group were minor, and largely related to mild phototoxicity managed conservatively. Other complications included cholangitis, hemobilia, cholecystitis, pancreatitis, duodenal perforation, hepatic abscess and myocardial infarction, and were a result of the endoscopic procedure and found in both groups treated[57].

Recently, Wiedmann *et al*[67] published their results using PDT as a neoadjuvant treatment for hilar cholangiocarcinoma. Seven patients were treated and underwent surgery after a median period of 6 wk (range, 3-44 wk). In all patients, tumor free resection margins were achieved with a 1-year recurrence free survival rate of 83%. Neoadjuvant PDT did not increase the rate of surgical complications and was well tolerated.

If PDT has become a standard of care in Europe, novel therapeutic approaches are still needed, such as a targeted molecular approach that may be used in conjunction to improve outcomes. For this therapy to become a more viable option alternative, photosensitizers are needed that provide deeper tumoricidal tissue penetration, shorter duration of phototoxicity, and more rapid onset[68].

CONCLUSION

In summary, the majority of patients with cholangiocarcinoma present with advanced, unresectable disease and treatment options remain limited. Photodynamic therapy in conjunction with stenting has shown very promising outcomes. Further multicenter, randomized, prospective controlled trials are needed to confirm the benefit of PDT and stenting compared to stenting alone, and to identify the optimal treatment regimen in these patients in order to improve their survival and quality of life.

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Staining for p53 and Ki-67 increases the sensitivity of EUS-FNA to detect pancreatic malignancy

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Abstract

AIM: To investigate whether tumor marker staining can improve the sensitivity of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) to diagnose pancreatic malignancy.

METHODS: Patients who underwent EUS-FNA were retrospectively identified. Each EUS-FNA specimen was evaluated by routine cytology and stained for tumor markers p53, Ki-67, carcinoembryonic antigen (CEA) and CA19-9. Sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (PLR and NLR) were calculated in order to evaluate the performance of each test to detect malignancy.

RESULTS: Sixty-one specimens had complete sets of stains, yielding 49 and 12 specimens from pancreatic adenocarcinomas and benign pancreatic lesions due to pancreatitis, respectively. Cytology alone had sensitivity and specificity of 41% and 100% to detect malignancy, respectively. In 46% of the specimens, routine cytology alone was deemed indeterminate. The addition of either p53 or Ki-67 increased the sensitivity to 51% and 53%, respectively, with perfect specificity, PPV and PLR (100%, 100% and infinite). Both stains in combination increased the sensitivity to 57%. While additional staining with CEA and CA19-9 further increased the sensitivity to 86%, the specificity, PPV and PLR were significantly reduced (at minimum 42%, 84% and 1, respectively). Markers in all combinations performed poorly as a negative test (NPV 26% to 47%, and NLR 0.27 and 0.70).

CONCLUSION: Immunohistochemical staining for p53 and Ki-67 can improve the sensitivity of EUS-FNA to diagnose pancreatic adenocarcinoma.

Key words: Endoscopic ultrasound; Fine needle aspiration; Pancreatic cancer; p53; Ki-67; Immunohistochemistry

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INTRODUCTION

Pancreatic cancer is the fourth highest cause of cancer death in the United States. The overall 5-year survival rate is less than 5%, although early detection and curative resection can improve the survival rate to 20%[1]. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has high specificity for malignancy in a solid pancreatic lesion, but sensitivity varies from 70% to 90%[2-14]. This is due to suboptimal sampling and cases of indeterminate cytology. It is difficult to distinguish well-differentiated cancers from reactive and benign cytologic changes. In such cases, tumor marker detection *via* immunohistochemistry (IH) may facilitate diagnosis. In this study, the diagnostic utility of p53, Ki-67, carcinoembryonic antigen (CEA), and CA 19-9 were assessed. The goal was to increase the sensitivity of EUS-FNA to diagnose malignancy without compromising specificity.

MATERIALS AND METHODS

Patients

Patients who underwent EUS-FNA in the years 2002 to 2008 at Harbor-UCLA Medical Center were retrospectively identified, and details were analyzed for demographic characteristics, presenting clinical features, laboratory data, imaging, and cytology results by chart review. Final diagnosis was established from: (1) tissue diagnosis consistent with malignancy; (2) imaging studies which included computed tomography (CT), magnetic resonance imaging (MRI), and EUS; and (3) clinical follow-up, including telephone calls, for at least 1 year.

Specimen acquisition and preparation

EUS-FNA was performed by 1 of 3 experienced endoscopists with a 22-gauge needle (Medi-Globe Inc or Wilson-Cook Inc) averaging 4 to 5 passes per session. The aspirate was immediately smeared onto a glass slide and fixed in 95% ethanol, and then sent to a cytopathologist for cytologic analysis. The residual material was fixed in 10% neutral buffered zinc formalin and embedded in paraffin for preservation in a cell block for IH labeling. Four micron sections of cell block were cut and deparaffinized, and two sections each were used for labeling with p53 (1:50; DO-7, Zymed), Ki-67 (1:50; MIB-1, DAKO), polyclonal CEA (1:50; Zymed), and CA19-9 (1:50; DAKO). Slides were pre-treated with 3% hydrogen peroxide in 100% methanol to block endogenous peroxidase activity and facilitate tissue permeability. The p53 and Ki-67 sections underwent further processing with heat for antigen retrieval: incubation EDTA solution (pH 8.0) at 100℃, followed by boiling water for 20-30 min. The reaction system was detected using the Signet-streptavidin peroxidase system, for one hour at 37℃. Finally, the reaction was developed with 0.5% diaminobenzidene in 0.05 mol/L Tris buffer, pH 7.4, containing 0.5% hydrogen peroxide, rinsed in tap water, counterstained with hematoxylin, dehydrated, cleared in xylene, and mounted in permanent cover slip medium.

Cytopathology

Cytologic smears and tissue cell blocks obtained by E US-FNA were reviewed by a cytopathologist who was blinded to the final diagnoses. For conventional cytology, the specimens were reported respectively as benign, indeterminate (atypical or suspicious for malignancy), or malignant. For IH, a positive result for malignancy was based on the following criteria for each stain: intense staining of pleomorphic nuclei for p53 (Figure 1A) and Ki-67 (Figure 1B), with additional criteria for greater than 50% of population stained for the latter, and intense and diffuse cytoplasmic staining by CA19-9 and polyclonal CEA.

Data analysis

Continuous variables were expressed as median and ra nge, and the Mann-Whitney U test was used to determine the statistical significance of differences between two groups. Fisher's exact test was used to determine statistical significance for categorical variables. A P value less than 0.05 was regarded as significant for both tests. To determine the discrimination of findings from cytology and IH, the sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (PLR and NLR) were calculated, each alone or in various combinations. Only specimens with complete sets of stains were included. Repeat samples were included. For the purposes of this study, atypical and suspicious specimens were deemed negative for malignancy

RESULTS

A total of 61 specimens with complete set of stains were identified, from 12 benign and 49 malignant cases on final diagnosis. Benign pancreatic lesions were due to chronic pancreatitis; of these, 3 cases were of autoimmune etiology. Malignant masses were due to pancreatic adenocarcinoma in all 49 cases. The patient demographic information, lesion location, and laboratory information on initial presentation are summarized in Table 1. Total bilirubin and CA19-9 levels were significantly higher in patients with cancer, but no other differences were detected.

Table 2 summarizes the positive staining results for the tumor markers p53, Ki-67, CEA and CA19-9, alone or in selected parallel combinations, according to their final diagnosis and cytologic findings. The sensitivity, specificity, PPV, NPV, PLR, and NLR with regard to the detection of pancreatic malignancy were calculated for cytology and each tumor marker, alone or in various combinations. Table 3 summarizes these results when applied to all the EUS-FNA specimens in selected combinations.

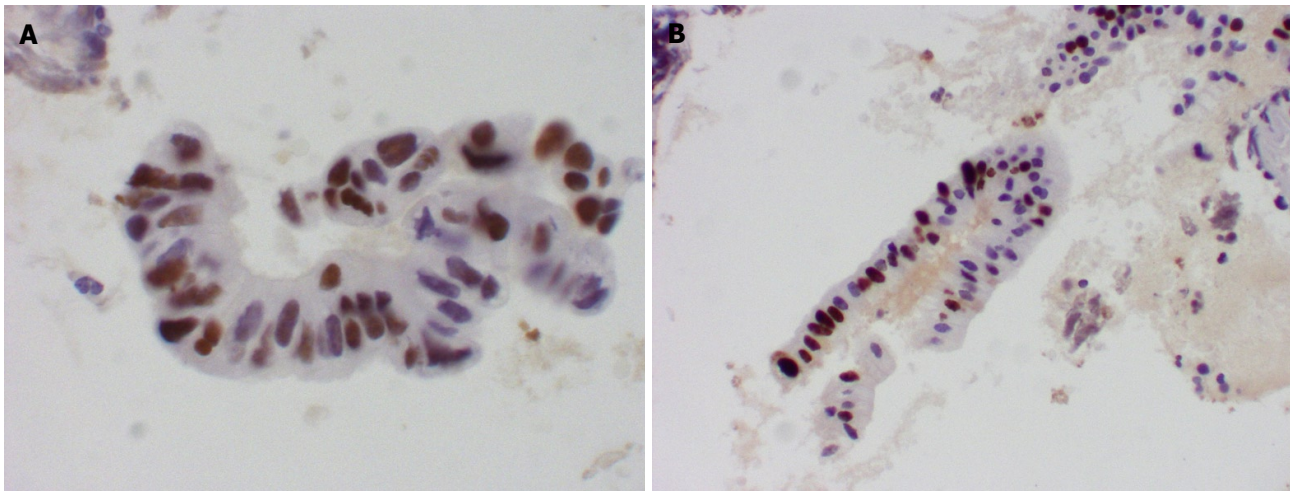

Figure 1 Immunoreactivity in pancreatic adenocarcinoma, counterstained with hematoxylin (blue), at 436 × magnification. A: Positive p53 staining of the pleomorphic nucleus (brown). B: Positive Ki-67 nuclear staining (brown), at greater than or equal to 50% of total cluster of cells.

Table 1 Patient data for those with pancreatic lesions definitively diagnosed as benign or malignant (not all laboratory data were available for each patient)

	Malignant (n = 49)	Benign (n = 12)
Age [median (range)]	61 (34-88)	60 (15-73)
Sex (M:F)	27:22:00	8:04
Location of pancreatic lesion		
Head/uncinate process	39	10
Body	9	2
Tail	1	0
Serum enzymes [median (range)]		
Total bilirubin[a] (mg/dL)	3 (1-28)	1 (0-5)
AST (U/L)	63 (11-603)	35 (13-182)
ALT (U/L)	74 (5-694)	33 (13-167)
ALP (U/L)	211 (54-1307)	136 (59-1409)
Amylase (U/L)	94 (15-182)	80 (11-285)
Lipase (U/L)	26 (13-199)	29 (16-95)
Serum tumor markers [median (range)]		
CEA (ng/mL)	5 (1-403)	3 (0-32)
CA19-9[a] (U/mL)	339 (0-9929)	28 (0-1507)

[a]$P < 0.05$, benign group compared with malignant. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CEA: carcinoembryonic antigen.

Routine cytology correctly diagnosed 20 of 49 cases to be malignant, with 8 false negatives. Twenty-eight specimens had indeterminate cytology (atypical or suspicious for malignancy), 46% of the total. They consti tuted 43% and 58% of malignant and benign specimens, respectively. With the assumption that the atypical and suspicious cases were benign, the sensitivity and specificity were 41% and 100%, respectively. If the suspicious specimens were deemed malignant, which proved to be so in our particular study, the sensitivity increased to 49%.

Parallel addition of each p53 or Ki-67 to cytology increased the sensitivity to diagnose malignancy by 10% and 12%, respectively. Both stains in combination further increased the sensitivity by 16%, to 57%. Two false negatives and 6 indeterminate cases were correctly diagnosed to be malignant. The specificity, PPV and PLR remained perfect (100%, 100% and infinite).

On the other hand, while addition of CEA and CA19-9 increased the sensitivity to 86%, their utility was compromised by their poor specificity. The high false positive rates at 58% and 25%, respectively, were due to indiscriminate staining of specimens with either indeterminate or benign cytology.

Table 4 summarizes the diagnostic yield for the same tests when applied only to EUS-FNA specimens that were found to be either benign or indeterminate on cytology (therefore only in specimens with non-malignant cytology). The overall trend was preserved.

DISCUSSION

EUS-FNA of the pancreas has an excellent specificity for cancer diagnosis, but its sensitivity is tempered by cases of suboptimal sampling and indeterminate cytology. In this study, routine cytology had sensitivity of 41%, which is much lower than previously reported (usual range 70% to 90%[2-14]). This was due to higher prevalence of indeterminate cytology at 46%, versus 4% to 26% reported in other studies[2-14]. The discrepancy is possibly due to instances of differing cytologic criteria having been applied to different patient populations. In agreement with this study, a retrospective study of 74 EUS-FNA specimens at another southern California hospital (Torrance Memorial Medical Center, Torrance CA) also had high incidence rate of indeterminate cytologies at 39%, yielding in a sensitivity and specificity of 52% and 100%, respectively[15]. (Procedures were performed by the endoscopist-coauthor VE, and slide evaluations

Table 2 Distribution of positive tumor marker stains, alone or in select parallel combinations, according to cytology and final diagnosis

Malignant ($n=49$)				Final diagnosis	Benign ($n=12$)			
Benign ($n=8$)	Atypical ($n=17$)	Suspicious ($n=4$)	Malignant ($n=20$)	cytology	Benign ($n=5$)	Atypical ($n=7$)	Suspicious ($n=0$)	Malignant ($n=0$)
1	4	0	9	p53	0	0	0	0
2	4	0	14	Ki-67	0	0	0	0
6	8	1	15	CEA	4	3	0	0
4	10	0	13	CA19-9	1	2	0	0
2	6	0	16	p53:Ki-67	0	0	0	0
6	12	1	17	p53:Ki-67:CEA	4	3	0	0
5	14	0	19	p53:Ki-67:CA19-9	1	2	0	0
6	15	1	19	All 4 stains	4	3	0	0

CEA: carcinoembryonic antigen.

Table 3 Diagnostic accuracy of routine cytology and immunohistochemistry, alone or in selected combinations, in detection of pancreatic cancer *via* endoscopic ultrasound-guided fine needle aspiration

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
Cytology	41	100	100	29	¥	0.59
p53 + cytology	51	100	100	33	¥	0.49
Ki-67 + cytology	53	100	100	34	¥	0.47
CEA + cytology	71	42	83	26	1	0.7
CA19-9 + cytology	69	75	92	38	3	0.41
p53+Ki-67 + cytology	57	100	100	36	¥	0.43
p53+Ki-67 + CEA+cytology	80	42	85	33	1	0.49
p53+Ki-67 + CA19-9 + cytology	80	75	93	47	3	0.27
All 4 stains + cytology	86	42	86	42	1	0.34

CEA: carcinoembryonic antigen; IH: immunohistochemistry; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

Table 4 Diagnostic accuracy of immunohistochemistry, alone or in selected combinations, as applied only to cytologically benign, atypical and suspicious specimens

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
p53	17	100	100	33	¥	0.83
Ki-67	21	100	100	34	¥	0.79
CEA	52	42	68	26	1	1.16
CA19-9	48	75	82	38	2	0.69
p53 + Ki-67	28	100	100	36	¥	0.72
p53 + Ki-67 + CEA	66	42	73	33	1	0.83
p53 + Ki-67 + CA19-9	66	75	86	47	3	0.46
All 4 stains	76	42	76	42	1	0.58

CEA: carcinoembryonic antigen; IH: immunohistochemistry; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

were done by pathologists at various University of California Medical Centers). These differences further emphasize the need for assessment beyond routine aspirate cytology.

This study shows that the detection of molecular tumor markers can increase the sensitivity of EUS-FNA to diagnose pancreatic malignancy, though this is tempered by variable reductions in their specificity. IH was utilized for their detection, as more advanced tests such as DNA mutation analysis, digital image analysis (DIA) and fluorescence *in situ* hybridization (FISH) are not routinely available, are much more expensive, need special preparation that sometimes necessitate larger samples, and have longer processing time.

By staining specimens with either benign or atypical cytology, the combination of both p53 and Ki-67 increased the pancreatic EUS-FNA sensitivity by 16%, and proved to be "pathognomonic" for malignancy with an infinite PLR. Of relevance, the abnormalities in both antigens have been correlated to the late stage of what is

now believed to be a step-wise progression from normal pancreatic epithelium to pancreatic intraepithelial neoplasia (PanIN), and then to frank adenocarcinoma[16,17].

Ki-67 is a proliferation antigen present in all phases of the cell cycle, except the resting phase[18]. The labeling index is directly correlated to the PanIN grade[17,19], and clear quantitative differences in labeling can be demonstrated between malignant and benign pancreatic lesions, most notably at higher cutoff points[20]. Findings from this study are consistent.

The tumor suppressor p53 controls cell cycle progression, differentiation and apoptosis[21,22]. It is inactivated largely *via* mutation, usually resulting in nuclear accumulation and positive IH stain[23-25]. The p53 abnormality is detected in 50% to 90% of pancreatic adenocarcinomas[23-31], and in their precursor, PanIN, the positive stain ing is directly correlated to the grade[17,29-31]. Our findings agree with previous studies on EUS-FNA of pancreas, which showed that the addition of p53 IH or DNA analysis resulted in a modest sensitivity gain[12-14]. Two notable differences were observed in comparison to other studies that have included the surgical specimen. First, in contrast to this study, false positive p53 stainings in be nign pancreatic lesions were demonstrated in previous studies at rates ranging from 3% to about 10%[12,13,26,27,31-33]. Indeed, wild-type p53 over-expression can be inducible under certain benign conditions, such as during inflammation in response to TNF-alpha[34]. Second, this study showed a lower rate of p53 IH positivity in malignant cases: 29% versus the usual range of 50% to 70% in other EUS-FNA and biopsy series[13,14,32]. There are multiple explanations for these discrepancies, such as the criteria used for positive p53 staining, but the most likely reasons are the relatively small patient group size and the over-representation of specimens with indeterminate cytology in our study.

CEA and CA19-9 staining resulted in non-significant PLRs due to dramatic reductions in specificity. Non-specific cytoplasmic staining with either CEA or CA19-9 has previously been demonstrated in both the normal and inflamed pancreatic ductal epithelium[35-37].

Performance was poor for all the markers when used as indicators for the absence of malignancy (alone or in various parallel combinations of up to four markers) as demonstrated by low NPVs and non-significant NLRs. This was due to suboptimal sampling, as well as the inherent limitations of IH to completely correlate marker accumulation and staining for their defect/mutation[23-25].Therefore, a negative test still necessitates further diagnostic measures to determine the presence or absence of malignancy.

There are a number of limitations to our study. First, not all patients had the "gold standard" - a surgical biopsy or autopsy - for definitive diagnosis. Second, only a limited number of specimens from benign pancreatic lesions were included in this study. Third, although not by design, non-ductal cancers and other neoplasias were not included in this study. This limits the scope of applicability. Fourth, in cytologically benign specimens that were later correctly diagnosed as malignant by either p53 or Ki-67 staning, two arguable scenarios exist: (1) that they were truly cases of missed cytologic diagnosis; or (2) that they were suboptimal samplings with false positive staining. It is beyond the scope of this study to distinguish between them. In conclusion, the addition of tumor marker staining by IH to routine cytology can increase the diagnostic yield of pancreatic EUS-FNA. In particular, staining for both p53 and Ki-67 gave the best overall performance and appears promising for future large prospective and studies.

COMMENTS

Background

Tissue sampling *via* endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has high specificity for the determination of malignancy of solid pancreatic lesions. But conventional cytologic examination alone can lead to either missed or ambiguous cases due to instances of suboptimal sampling and indeterminate cytology. This leads to delayed diagnosis and therapy, along with increased cost, mortality and morbidity, resulting from the necessity for further diagnostic procedures.

Research frontiers

Molecular changes associated with carcinogenesis may help to diagnose malignancy of a pancreatic lesion where routine cytologic examination of EUS-FNA samples alone is inadequate. Four well-characterized tumor markers detected by immunohistochemistry, p53, Ki-67, carcinoembryonic antigen and CA19-9, were used along with routine cytology to increase the sensitivity of EUS-FNA.

Innovations and breakthroughs

This paper shows that the use of tumor markers p53 and Ki-67 can increase the sensitivity of EUS-FNA while maintaining 100% specificity, if used with select criteria. Furthermore, immunohistochemistry is a much more cost-effective approach in comparison to other more advanced cytologic/molecular techniques, such as digital image analysis, fluorescence *in situ* hybridization, or direct DNA mutation analysis *via* polymerase chain reaction.

Applications

This study shows that the addition of tumor markers detected *via* immunohistochemistry can increase the pancreatic cancer rate detection of EUS-FNA. This leads to faster diagnosis and therapy, with fewer and less costly diagnostic procedures being needed, which may ultimately lead to a decrease in morbidity and mortality associated with pancreatic lesions. Prospective studies with larger number of cases are needed for validation.

Peer reviews

This seems like a good study showing that sensitivity for pancreatic tumor detection can be increased from 41% to 57% using p53 and Ki-67 staining on EUS-guided FNA specimens. The author appropriately admits to loss of specificity with use of multiple stains. This is an interesting twist on current technology and should be published.

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CASE REPORT

Small bowel parasitosis as cause of obscure gastrointestinal bleeding diagnosed by capsule endoscopy

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Abstract

Hookworm infection is a relatively common cause of anemia in endemic areas. However, it is rarely encountered in Europe. In this report we describe the case of a 24-year old patient originating from an endemic area who was admitted due to severe anemia, with an Hct of 15.6% and eosinophilia (Eosinophils: 22.4%). While both esophagogastroduodenoscopy and colonoscopy were non-diagnostic, capsule endoscopy revealed a large number of hookworms infesting his small bowel and withdrawing blood. The patient was successfully treated with Albendazole. Capsule endoscopy was proven an important tool in diagnosing intestinal parasitosis.

Key words: Ancylostoma duodenale; Parasitosis; Capsule endoscopy; Obscure gastrointestinal bleeding; Anemia

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INTRODUCTION

Hookworm infection represents a major burden of disease in the developing world, with many cases of iron deficient anemia being caused by this type of parasitosis. In this report we present the case of a young man originating from South-East Asia, whose hookworm infection was diagnosed by capsule endoscopy, providing high-quality images of the disease processes taking place inside the patients' gut.

CASE REPORT

A 24-year old Pakistani man who immigrated to Greece one year ago was referred to our hospital for small bowel capsule endoscopy. The patient was initially admitted to another hospital complaining for worsening fatigue. On his admission severe anemia was diagnosed [Hct: 15.6% (normal 41%-53%), Hb: 2.3 mmol/L (8.4-10.9 mmol/L) MCV: 62.9 fl (78-100 fl)] along with marked eosinophilia [Eosinophils: 22.4% (0%-8%), WBC: 7.02 × 10^9/L

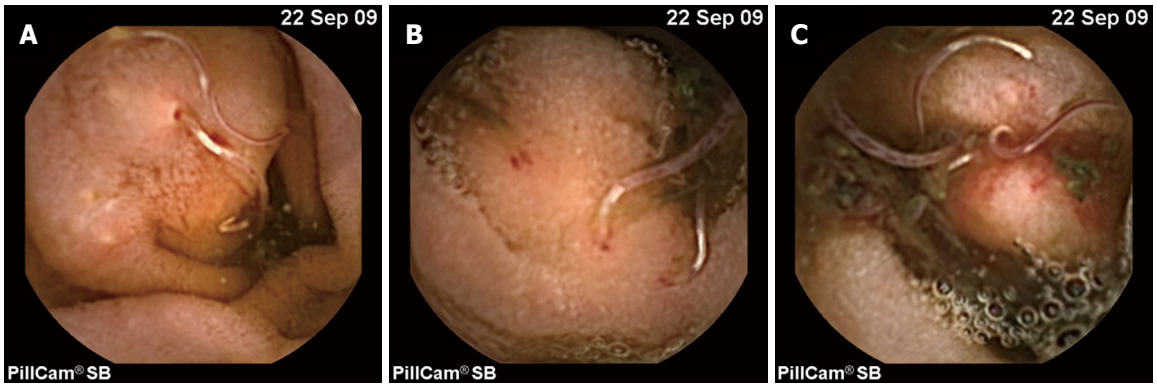

Figure 1 Hookworms infestating the patient's small bowel as seen with capsule endoscopy. A: Hookworms attached onto the mucosal surface, withdrawing blood, which can be seen inside their gut; B,C: Bleeding caused by the parasites.

(4.5-11 × 10^9/L)]. Physical examination was unremarkable apart from signs of anemia. He was assessed by EGD, colonoscopy, along with transabdominal ultrasound and numerous blood tests. The results were normal, apart from the aforementioned anemia and eosinophilia. Stool test showed no ova or parasites.

The capsule endoscopy performed in our department (Pillcam SB capsule, Given Imaging, Yoqneam, Israel) revealed a large number of hookworms infesting the patient's small bowel (Figure 1A) from the duodenum to the proximal ileum. The parasites were attached to the mucosal surface of the intestine withdrawing blood, whereas mucosal bleeding was seen in areas previously attacked by the parasites (Figure 1B, C).

The patient was treated with a single dose of 400 mg of albendazole[1] and oral iron supplementation. His hemoglobin and hematocrit substantially improved in the following 2 wk and were normal in a follow up visit 4 mo later.

DISCUSSION

Hookworm infection in human subjects is caused by the helminth nematodes Necator americanus and Ancylostoma duodenale, both of which are strictly human parasites[1]. An estimated 576-740 million people are infected, especially in poor, rural areas in the tropics and subtropics, making hookworm infection one of the most common chronic infections worldwide[2]. N. americanus is found in the Americas, the Caribbean and has recently been reported in Africa, Asia and the Pacific. A. duodenale infections are common in sub-Saharan Africa, Asia and the Pacific[3,4]. Both types of hookworms parasitise the proximal part of the small intestine in their adult form. The daily output of eggs per female worm is around 10000 for N. americanus and can be as high as 30000 for A. duodenale. Eggs hatch in soil. The larvae molt twice to become infective third-stage larvae, which penetrate the host's skin, travel through the circulation, reach the alveolar capillaries, enter the lungs, pass over the epiglottis and are swallowed into the gastrointestinal tract. A. duodenale can also be infective when ingested as third-stage larvae[5]. Our patient originated from South-East Asia, an area where A. duodenale is endemic. However, the identification of the exact type of hookworm is not easy by just viewing the capsule endoscopy images.

Iron deficient anemia is the main adverse outcome of hookworm infection. Blood loss occurs when the parasites attach themselves onto the mucosal surfaces using their cutting apparatus and contract their muscular esophagi to create negative pressure, which allows the withdrawing of blood. In addition, adult hookworms also release anticlotting agents to ensure blood flow[6,7]. The hookworms ingest a portion of the extravasated blood and red cells undergo lysis releasing hemoglobin, which is digested by enzymes that line the parasites' gut[5,8]. All these processes can be visualized in the images presented. Areas of bleeding can be seen in previously attacked areas of the mucosa, while the parasites' gut containing blood can be readily visualized. The patient presented, had severe anemia. The presence of more than 40 adult hookworms has been reported to be adequate to cause a host hemoglobin level of less than 6.82 mmol/L, especially if the initial iron stores of the host were not adequate[9].

Eosinophilia can also be detected in 30% to 60% of cases[3] and its peak usually coincides with the development of adult hookworms in the intestine, which in turn occurs 5 to 9 wk after the onset of the infection[10]. Our patient immigrated to Greece almost a year ago and it seems unlikely that his eosinophilia represents the stage of adult hookworm formation. Rather, it probably reflects the state of chronic eosinophilia of the parasitic infection.

The diagnosis of hookworm infestation is normally based on the microscopical examination of feces to detect hookworm eggs[5]. However in this case, stool microscopy failed to identify any eggs. This was also the case in some other instances of hookworm infections diagnosed by capsule endoscopy[11-14]. It seems however that this is the first such endoscopically proven case reported in Europe. Capsule endoscopy provided us with a better insight into the processes taking place in this disease entity. In addition, this case underscores the importance of parasites as the cause of disease, even in non endemic areas.

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CASE REPORT

Endoscopic extraction of a metal key impacted within the appendix

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Abstract

Ingested foreign bodies are rarely impacted in the appendix. They may be clinically latent or cause complications such as appendicitis or intestinal perforation, thus requiring prompt and appropriate therapy. A case is reported of a psychiatric, but in other respects asymptomatic, patient who presented with an ingested metal key deeply impacted within the appendix. The patient underwent urgent coloscopy for retrieval. Initially all conventional endoscopic instruments proved ineffective and the key was finally extracted using a simple manoeuvre, described herein.

Key words: Foreign body; Ingested; Appendix; Impaction; Endoscopic extraction

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Pilichos C, Tasias G, Pyleris E, Anyfantis N, Pantelaros N, Barbatzas C. Endoscopic extraction of a metal key impacted within the appendix. *World J Gastrointest Endosc* 2010; 2(11): 372-374 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i11/372.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i11.372

INTRODUCTION

The passage of ingested foreign bodies through the gastrointestinal tract is uneventful in the great majority of cases. Complications, including bowel wall penetration, peritonitis or enteric obstruction, occur rarely. They are more frequent if the ingested objects are long and sharp such as chicken or fish bones, toothpicks and needles which tend to impact at sites of anatomical narrowing (pylorus, ligament of Treitz, ilio-cecal valve or recro-sigmoid junction). We report our experience with a patient presenting with an asymptomatic impaction of a metallic key within the appendix which was successfully managed by coloscopy.

CASE REPORT

A 44 year old woman was transferred from a psychiatric clinic to our hospital presenting with mild abdominal pain following the reported ingestion of a metal key 4 d previously.

The patient was in good clinical condition; all laboratory tests were normal. Abdominal x-rays confirmed the pre sence of the ingested key in the right iliac fossa (Figure 1).

Soon after her admission, the patient underwent urgent coloscopy without previous bowel preparation. The ingested object was found in the bottom of the cecum, deeply impacted in the appendix (Figure 2). Despite the use of conventional instruments for endoscopic foreign

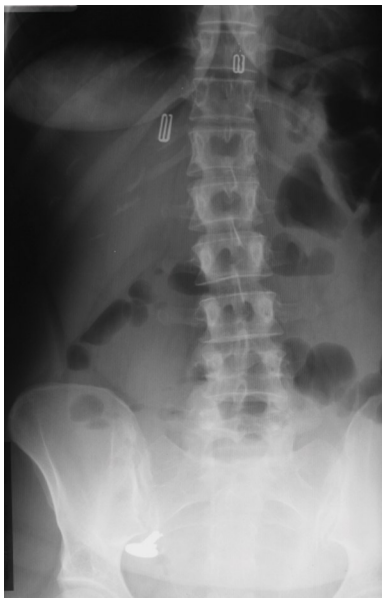

Figure 1 Plain abdominal X-ray revealing the presence of a metal key in the right lower quadrant.

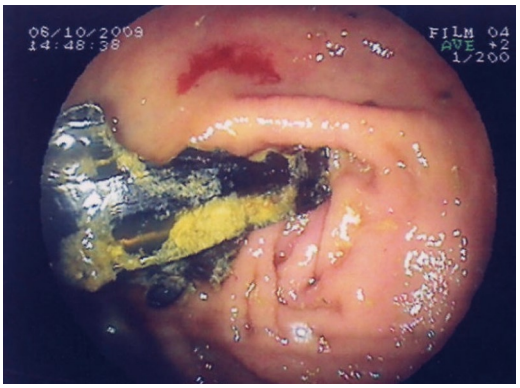

Figure 2 Endoscopic view of the object which is impacted in the appendiceal orifice.

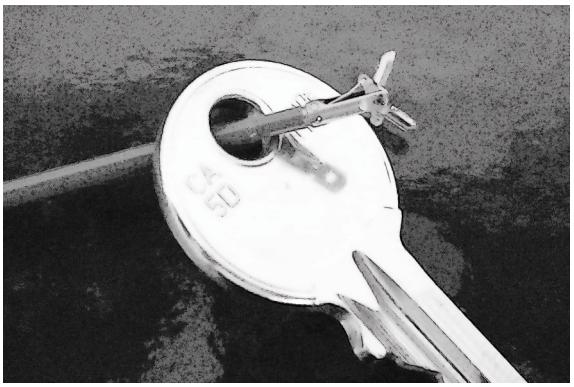

Figure 3 Schematic reconstruction depicting a regular biopsy forceps, inserted through the hole in the handle of the key. Once the "jaws" opened, the forceps served as a "hook" for the extraction of the key.

body extraction (polypectomy snare, alligator and rat tooth forceps, Dormia and Rothnet baskets), all attempts proved ineffective.

Finally we tried the following manipulation: we inserted a biopsy forceps through the hole in the handle of the key, kept the jaws of the forceps open using them as hooks and with gentle traction the impacted key was gradually moved in the cecum (Figure 3). The subsequent extraction through the anus was easily accomplished without complications.

DISCUSSION

Appendiceal impaction of an ingested foreign body is exceptional. It was described for the first time in 1759 and most cases were published before 1900, due to social habits such as hand sewing and wild game consumption. Depending on their shape and consistence, foreign bodies that impact in the appendix may cause appendicitis, abscess or intestinal perforation. Hydronephrosis and lead poisoning have also been reported[1-4]. Blunt foreign bodies such as keys and prosthetic teeth are likely to remain dormant for long periods and cause appendicitis through late obstruction of the appendiceal lumen. Thus, the object retrieval is indicated independently of clinical symptoms and time of diagnosis[4,5].

Traditionally, foreign body impaction in the lower gastrointestinal tract has been treated by early surgery. The appendix is no exception but this approach to management should be reconsidered as the technical equipment and skills of endoscopists have evolved[6,7]. Moreover, Selivanov *et al*[8] reporting a 10 year experience of 100 consecutive patients concluded that surgery might represent an overtreatment in this setting.

Colonoscopic removal of foreign bodies impacted in the appendix seems an efficacious and safe therapeutic method. According to a pragmatic algorithm recently proposed by Klingler, it should be attempted in patients without serious complications and for foreign objects radiographically localized in the right lower quadrant whose anatomical position seems unchanged during a three day follow-up. If this is unsuccessful however, laparoscopic exploration with fluoroscopic guidance should be carried out to localize and remove the objects either by ileotomy, colotomy or by appendectomy[9].

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CASE REPORT

Placement of a fully covered self-expandable metal stent in a young patient with chronic pancreatitis

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Abstract

Plastic stent insertion is a treatment option for pancreatic duct stricture with chronic pancreatitis. However, recurrent stricture is a limitation after removing the plastic stent. Self-expandable metal stents have long diameters and patency. A metal stent has become an established management option for pancreatic duct stricture caused by malignancy but its use in benign stricture is still controversial. We introduce a young patient who had chronic pancreatitis and underwent several plastic stent insertions due to recurrent pancreatic duct stricture. His symptoms improved after using a fully covered self-expandable metal covered stent and there was no recurrence found at follow-up at the outpatient department.

Key words: Chronic Pancreatitis; Pancreatic duct stricture; Fully covered self-expandable metal covered stent; Young patient

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Lee KJ, Kim KJ, Shin DH, Jung JW, Park JY, Bang SM, Park SW, Song SY. Placement of a fully covered self-expandable metal stent in a young patient with chronic pancreatitis. *World J Gastrointest Endosc* 2010; 2(11): 375-378 Available from: URL: http://www.wjgnet.com/1948-5190/full/v2/i11/375.htm DOI: http://dx.doi.org/10.4253/wjge.v2.i11.375

INTRODUCTION

The treatment of chronic pancreatitis with pancreatic duct stricture is still challenging. Conventional plastic pancreatic duct (PD) stents are unsatisfactory because of recurrent stricture and pain. Recently, self-expandable metal covered stents (SEMS) have been used to treat strictures of the main pancreatic duct in chronic pancreatitis patients. However, its long-term safety and efficacy are uncertain because of epithelial hyperplasia and migration[1]. Some studies have demonstrated that a fully covered SEMS (FCSEMS) was effective in patients with symptomatic refractory PD stricture[2]. Here, we introduce a young patient with refractory PD stricture caused by chronic pancreatitis; the stricture and pain were effectively treated after placement of FCSEMS.

CASE REPORT

A 13 year old male visited Severance Hospital, Yonsei

University College of Medicine with complaints of recurrent abdominal pain. He was diagnosed with chronic pancreatitis at the age of twelve. Magnetic resonance cholangiopancreatography (MRCP) showed chronic pancreatitis and a benign cystic lesion at the pancreatic groove, suggestive of pseudocyst (2.7 cm) (Figure 1). For the treatment of pancreatic pseudocyst, a cysto-duodenal stent (double pigtail, 4 cm) was inserted. One month later, computed tomography (CT) scan showed resolution of the cyst. At three months, the stent had disappeared on CT and no further treatment was provided as he had no symptoms. However, he returned with abdominal pain and vomiting six months after the first trial of the stent. CT showed pancreatic duct dilatation with multiple persistent parenchymal or intraductal calcification, especially at the head of pancreas head, and aggravation of pseudocyst. A plastic PD stent (7 Fr, 5 cm) was inserted and then removed two months later. Another stent of the same size was re-inserted as CT scan showed a remaining cyst. Four months later, pancreatogram showed diffuse dilatation of the pancreatic duct and filling defects at the pancreatic head. A new PD stent with a larger diameter (10 Fr, 5 cm) was inserted. He did not show any symptoms and was admitted to the hospital six months later during his winter break. The CT scan showed resolution of the cyst. However, after removing the stent, pancreatogram showed an irregular stricture and proximal duct dilatation at the main pancreatic duct and pancreatic duct stones were found. Emergent mechanical lithotripsy was used for the treatment of pancreatic stones and the stones were partially removed. He underwent extracorporeal shock wave lithotripsy (ESWL) in the urology department for two days and endoscopic retrograde cholangiopancreatography (ERCP) was done on the day after the last ESWL. The finding still showed PD stones with reduced number and sizes. A plastic PD stent (10 Fr, 5 cm) was inserted for the treatment of pancreatic duct stricture and stones. Four months after inserting the last plastic stent, ERCP showed no definite stricture at the pancreatic duct and the patient was followed up without additional stent insertion. Three months later, he again complained of abdominal pain. ERCP showed that the pancreatic duct was markedly dilated with a stenosis of the head portion but without stones. To use a larger and more expandable device, a removable metal stent (Niti-S type biliary stent, covered, 10 mm, 5 cm, Taewoong, Seoul, Korea) was inserted into the pancreatic duct (Figure 2A). There were no procedure related complications. The patient recovered and was discharged after two days. The follow-up ERCP was performed 1 mo after the stent placement and the stent was successfully removed with an elegator (Figure 2B). After removal of the stent, the pancreatic duct stricture was much improved. Fifteen months after the stent removal, ERCP showed that the patency of the pancreatic duct was maintained (Figure 2C). The patient remains healthy without any signs or symptoms of pancreatitis or need for any pancreatic enzyme supplement or narcotics at 24 mo after stent removal.

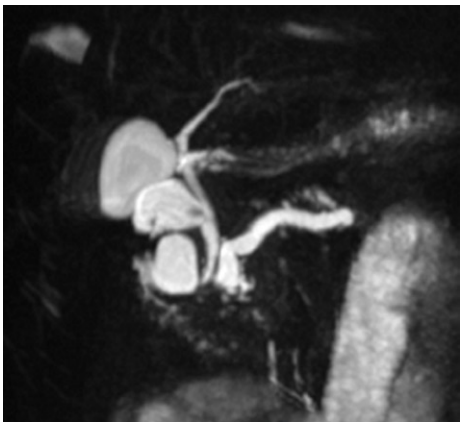

Figure 1 Initial magnetic resonance cholangiopancreatography showed chronic pancreatitis and pseudocyst.

DISCUSSION

About 50% of patients with severe chronic pancreatitis undergoing endoscopic treatment require pancreatic stent placement in order to relieve obstruction of the main pancreatic duct. Even though endoscopic placement of plastic stents has been widely used, it has several limitations[3-5]. For example, since the plastic stents often become occluded with sludge, they usually need to be changed every 3 to 4 mo[6]. Thus, the number of procedures, hospitalization and costs may increase. As an alternative treatment for blockages of plastic stent or refractory stricture after the plastic stent removal, the placement of a metal stent has been considered. Metal stents have a longer patency than polyethylene stents and usually a single metal stent can palliate obstruction for good. The metal stent is effectively used in the treatment of malignant pancreatic duct obstruction. In contrast, its use in patients with benign diseases has yet to be well-established. There have been only a few studies regarding long-term complications, efficacy and outcomes with the use of metal stent in benign disease[7]. In our study, the patient underwent removable metal stent insertion and remained not just free from pain but also had no recurrence of pancreatitis for more than 2 years after the removal of the metal stent. A follow-up pancreatogram also showed resolution of dominant pancreatic ductal strictures. So far, results of self-expandable uncovered metal stents had been disappointing with regard to poor drainage of pancreatic juice and difficult removal due to tissue ingrowth[1,8]. Some studies even recommended that, considering complications such as increasing cancer risk or stent migration, SEMS should not be placed in patients with a benign gastrointestinal disorder, a long life expectancy and who are good candidates for surgery. To overcome these limitations, FCSEMS was developed. A FCSEMS with a larger diameter (up to 6 or 8 mm) may have an advantage in resolving or improving pancreatic ductal stricture compared with a single plastic stent[9]. In addition, the Niti-S type biliary stent (covered, Taewoong) used in this case has a double coated silver membrane

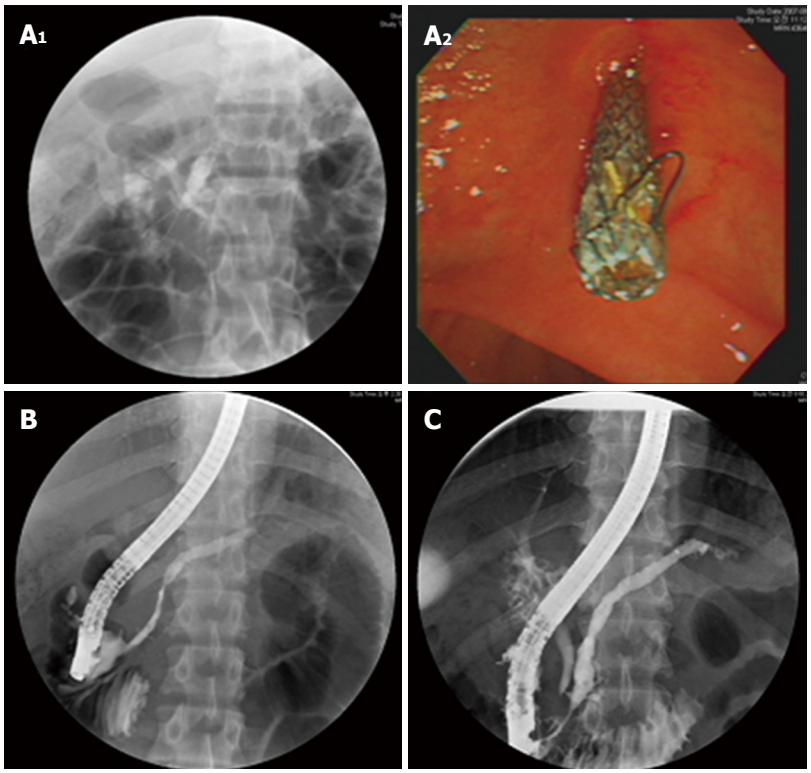

Figure 2 Fully covered self-expandable metal stent. A: Niti-S type biliary covered stent was inserted; B: Metal stent was removed; C: Follow-up endoscopic retrograde cholangiopancreatography showed that the pancreatic duct was patent.

which prevents direct contact of the metal with tissue, causes less tissue embedding and can be easily removed. Primary placement of an FCSEMS may, therefore, be an attractive option for refractory benign pancreatic ductal strictures.

Recently, Park *et al*[9] showed that placement of FC SEMS in patients with refractory benign pancreatic ductal strictures for 2 mo might be feasible and relatively safe. Moon *et al*[10] reported that temporary 3 mo placement of modified FCSMS with anti-migration features was effective in resolving pancreatic duct strictures in chr onic pancreatitis and reduced stent migration. Theoretically, they could provide better drainage and easy removability. However, in their reports, pancreatic sepsis or infection and cholestatic liver dysfunction were still common complications caused by metal stents. Even though FCSEMS seems to be promising, more tech nological improvement is needed before applying FCSEMS in benign pancreatic diseases in order to be accepted by more endoscopists. Also, further long-term fo llow-up studies are needed to determine the optimal duration and diameter of FCSEMS for refractory benign pancreatic ductal strictures.

In this case study, a temporary 1 mo placement and removal of a FCSEMS in the main pancreatic duct was deemed feasible and relatively safe. Moreover, the patient had no complications. We expect wider usage of metal stents in benign pancreatic diseases after confirming its long-term efficacy and determining the optimal duration of FCSEMS placement for refractory benign pancreatic ductal strictures through studies with a large number of patients.

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Cytomegalovirus gastritis

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Abstract

Cytomegalovirus (CMV) has been increasingly recognized as an important common pathogen in an immunocompromised state. The colon and stomach are the most common sites of its gastrointestinal infection. Symptoms of CMV gastritis are usually nonspecific and include epigastric pain, fever, nausea and bleeding. Endoscopic features are quite variable and include macroscopically normal mucosa, diffuse erythema, nodules, pseudotumors, erosions and ulcers. The bioptic detection of intranuclear inclusions is the hallmark of CMV infection. Most gastrointestinal CMV infection responds well to ganciclovir. We present endoscopic and histopathological features of CMV gastritis in a 71 year old woman receiving long-term prednisolone for pemphigus vulgaris.

Key words: Cytomegalovirus; Gastritis; Pemphigus vulgaris; Endoscopy

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TO THE EDITOR

A 71 year old woman who had been receiving long-term prednisolone for pemphigus vulgaris underwent upper gastrointestinal endoscopy for screening. She denied ha ving abdominal symptoms. On examination, there was no tenderness on abdominal palpation and normal bowel sounds. Endoscopic examination revealed numerous patchy erythemas in the gastric body (Figure 1A). The erythema was slightly depressed (Figure 1B). The histopathological examination of the lesion showed large epithelial cells with characteristic "owl's eye" eosinophilic intranuclear inclusion body surrounded by a clear halo (Figure 1C) compatible with cytomegalovirus (CMV) infection. Positive immunostaining for CMV antigens confirmed the diagnosis of CMV gastritis (Figure 1D). The gastritis improved with the treatment of ganciclovir.

CMV has been increasingly recognized as an important common pathogen in an immunocompromised state including those caused by immunosuppressive medications, cancer chemotherapy, transplant recipients, aging and human immunodeficiency virus infection[1]. The colon and stomach are the most common sites of its gastrointestinal infection. Although postural epigastric pain has been described as a sign of CMV gastritis[2], symptoms of

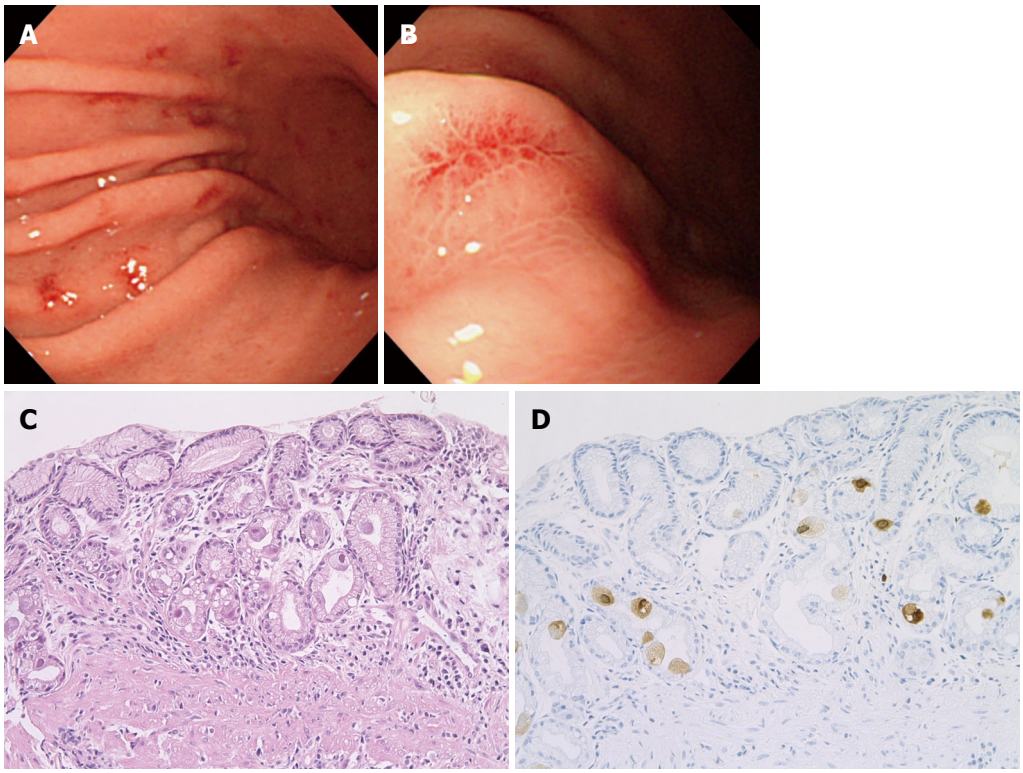

Figure 1 Endoscopic and histopathological pictures of cytomegalovirus gastritis. A: Note numerous patchy erythemas in the gastric body; B: Closer observation showing the slightly depressed erythema; C: Histopathological examination of the erythema showing large epithelial cells with characteristic "owl's eye" eosinophilic intranuclear inclusion body surrounded by a clear halo (H&E, × 200); D: Note positive immunostaining for cytomegalovirus antigens × 200).

this disorder are usually nonspecific and include epigastric pain, fever, nausea and bleeding. Endoscopic features are quite variable and include macroscopically normal mucosa, diffuse erythema, nodules, pseudotumors, erosions and ulcers. Although the bioptic detection of "owl's eye" is the hallmark of CMV infection, classical intranuclear inclusions are not always found because CMV may infect vascular endothelium or connective tissue stromal cells under the ulcers as well as mucosal epithelium[3]. Therefore, several diagnostic tools have been coupled for the suspected infection including CMV antigenemia assay and polymerase chain reaction of the specimen[4,5]. Most gastrointestinal CMV infection responds well to ganciclovir regardless of the cause of the underlying immunosuppression.

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Meetings

Events Calendar 2010

January 25-26
Tamilnadu, India
International Conference on Medical Negligence and Litigation in Medical Practice

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

February 11-13
Fort Lauderdale, FL, United States
21th Annual International Colorectal Disease Symposium

February 26-28
Carolina, United States
First Symposium of GI Oncology at The Caribbean

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-17
Landover, Maryland, United States
12th World Congress of Endoscopic Surgery

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

April 28-May 01
Dubrovnik, Croatia
3rd Central European Congress of surgery and the 5th Croatian Congress of Surgery

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 15-19
Minneapolis, MN, United States
American Society of Colon and Rectal Surgeons Annual Meeting

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

June 20-23
Mannheim, Germany
16th World Congress for Bronchoesophagology-WCBE

August 28-31
Boston, Massachusetts, United States
10th OESO World Congress on Diseases of the Oesophagus 2010

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 11-12
La Jolla, CA, United States
New Advances in Inflammatory Bowel Disease

September 16-18
Prague, Czech Republic
Prague Hepatology Meeting 2010

September 23-26
Prague, Czech Republic
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases

October 07-09
Belgrade, Serbia
The 7th Biannual International Symposium of Society of Coloproctology

October 15-20
San Antonio, TX, United States
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting

October 23-27
Barcelona, Spain
18th United European Gastroenterology Week

October 29-November 02
Boston, Massachusetts, United States
The Liver Meeting® 2010--AASLD's 61st Annual Meeting

November 13-14
San Francisco, CA, United States
Case-Based Approach to the Management of Inflammatory Bowel Disease

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Instructions to authors

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and

Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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