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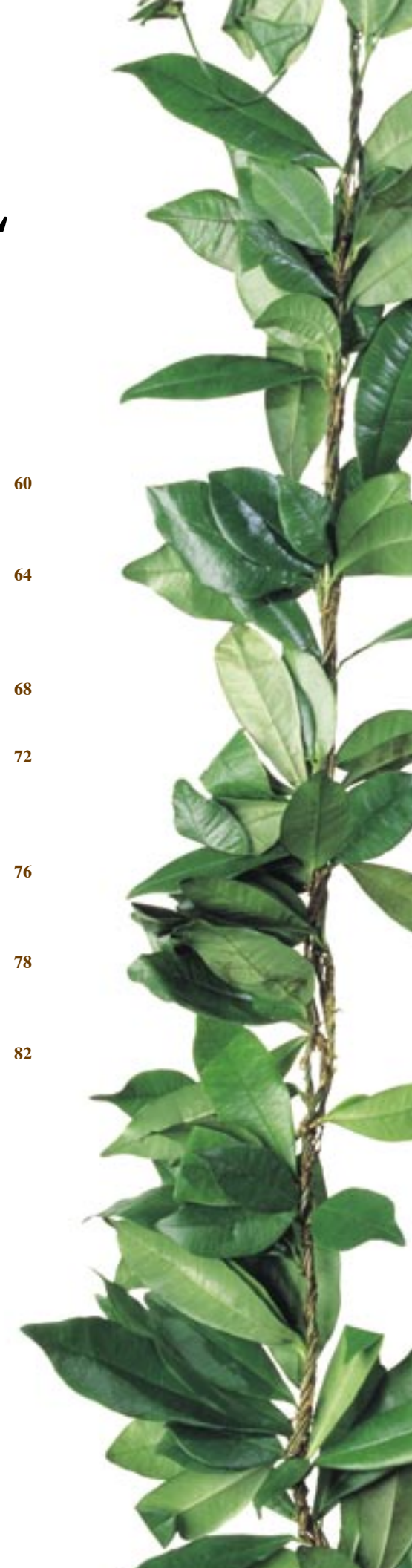

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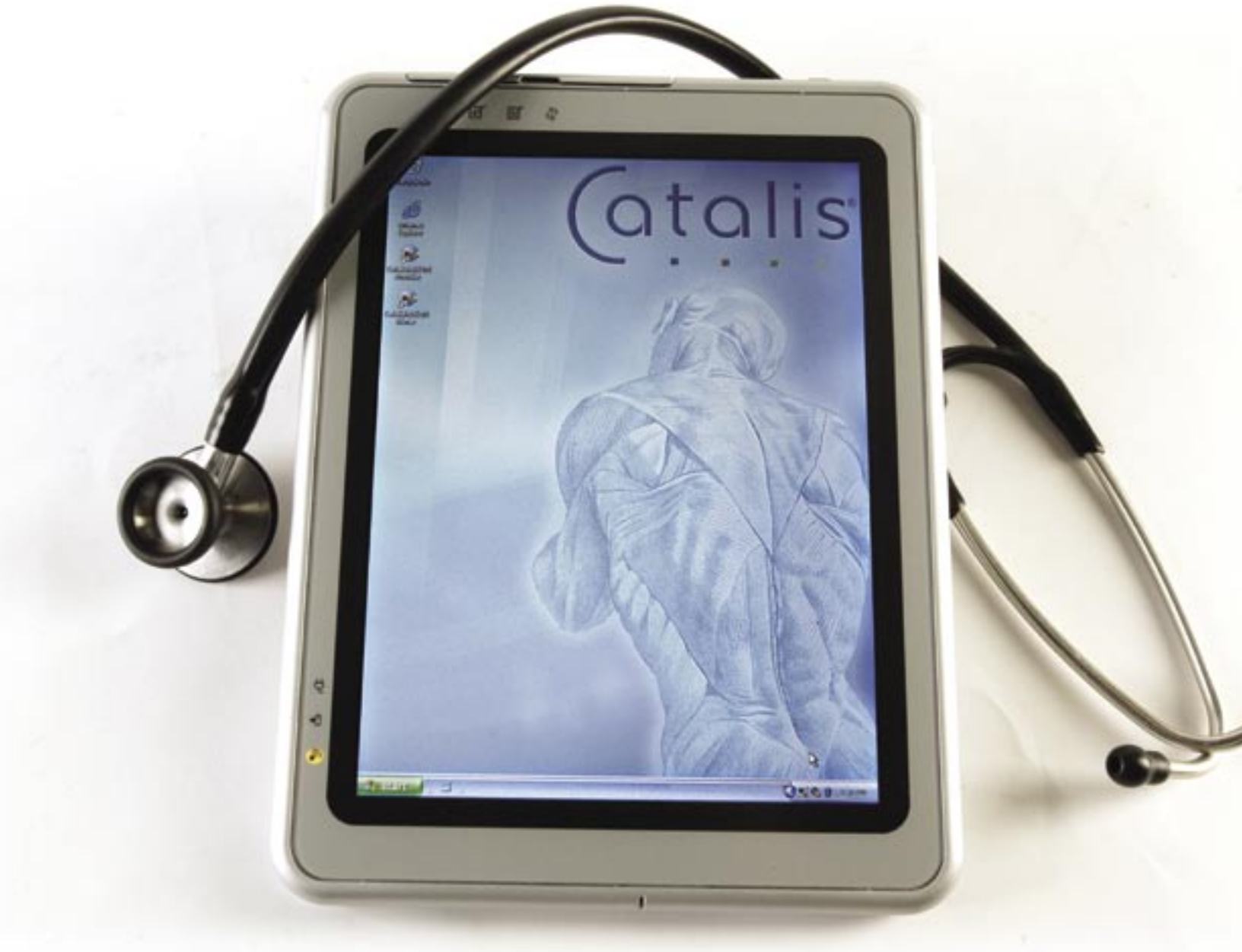

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Thyrotoxic Periodic Paralysis in a Polynesian Male Following Highly Active Antiretroviral Therapy for HIV Infection

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Abstract

Hyperthyroidism has been described after highly active antiretroviral therapy for AIDS and has been attributed to late onset immune reconstitution. The team reports a young Polynesian man with AIDS who responded to highly active antiretroviral therapy. However, 15 months after initiation of antiretroviral therapy, he was hospitalized for hypokalemic thyrotoxic periodic paralysis, an unusual manifestation of hyperthyroidism which typically occurs in young Asian males.

Introduction

Thyrotoxic periodic paralysis (TTP) is an uncommon but well described complication of hyperthyroidism,[1] particularly among young Asian males.[2,3] We describe herein a young Polynesian man who presented with TTP due to Graves disease as a late complication of highly active antiretroviral therapy for AIDS.

Case Report

A 27-year-old Polynesian man with AIDS was admitted to Queen's hospital because of chronic diarrhea and one day of bilateral leg weakness. Four years prior to admission (PTA) he was diagnosed with AIDS complicated by CNS toxoplasmosis and pneumocystis pneumonia. He received sporadic antiretroviral therapy until two years PTA when he was seen by an HIV physician. At that time his HIV serology was positive by Western blot, his CD4 lymphocyte count was 19/mm^3 (1%) and his HIV load was 517,000 copies/mL. Fifteen months PTA, he was placed on highly active antiretroviral therapy (HAART) consisting of Combivir (lamivudine/zidovudine) and Kaletra (lopinavir/ritonavir). One month PTA his CD4 lymphocyte count had increased to 206/mm^3 and his HIV viral load had decreased to less than 50 copies/mL.

Approximately three months PTA he began having 2-3 loose bowel movements per day, which increased to 3-5 times per day one week PTA. One day PTA he became nauseated and vomited three times, followed by generalized weakness that caused him to fall several times. On the morning of admission he was too weak to get out of bed and was admitted to our hospital.

He was married and denied male-to-male sex, IV drug abuse, or blood transfusion, but he had had tattoos in the past. He denied any family history of muscle weakness, paralysis, or thyroid disease. His appetite was good but he had lost 15 kg over the past six months.

Physical examination on admission revealed an alert, muscular, healthy-appearing man in no distress. His temperature was 36.9°C, heart rate 96 beats/minute, respiration rate 16/minute, and blood pressure 142/76 mmHg. His weight was 99.8 kg and height 179 cm (BMI=31.2). Neurological examination showed grade 3/5 strength of both lower extremities and grade 4/5 strength of both upper extremities. Deep tendon reflexes were 1+ in all extremities.

Admission serum chemistry levels were: sodium 139 mEq/L, potassium 2.2 mEq/L, chloride 104 mEq/L, bicarbonate 26 mEq/L, BUN 7 mg/dL, creatinine 0.6 mg/dL, albumin 3.5g/dL, magnesium 1.3 mg/dL, phosphorus 3.8 mg/dL, and calcium 9.2 mg/dL. An ECG showed sinus tachycardia but no ST segment or T wave changes. Stool examinations for leukocytes, ova & parasites, including cryptosporidium, cyclospora, mycobacteria, blastocystis, CMV, salmonella, shigella, campylobacter, and *C. difficile,* were all negative.

Hospital Course

His hypokalemia was initially attributed to intestinal losses. His weakness resolved within an hour after replacement of potassium chloride 20 mEq intravenously and 40 mEq orally. On the day after admission, further questioning revealed that, in addition to increased frequency of bowel movements, he had noticed several months of increased appetite, heat intolerance, sweating, irritability, palpitations, and shortness of breath. For the past month he had noticed leg weakness and difficulty rising from a squatting position. Examination revealed persistent tachycardia up to 108 beats/min, temperature 37.1°C, blood pressure 152/83 mm of Hg, and a respiratory rate of 24/min. A fine tremor of the fingers was present.

Thyrotoxic periodic paralysis (TPP) was suspected. An endocrinology consultant described the thyroid as symmetrical, normal in size, and non-tender. There was a bruit in the right side of the neck. His conjunctivae

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were injected, but he had no proptosis or lid lag. His precordium was hyperdynamic. Acanthosis nigricans was present on the neck and in the axillae. Further laboratory evaluation revealed a decreased serum TSH of 0.02 uU/mL (normal 0.28-4.02), and an elevated free T4 of 4.4 ng/dL (normal 0.6-1.7). The thyroid radioiodine uptake was increased to 50% at 5 hours and 56% at 23 hours, and the thyroid scan was consistent with Graves' disease.

He was treated with supplemental oral potassium as well as propanolol to relieve his symptoms of Graves' disease and TPP. One week after discharge he was seen in the outpatient clinic and he had no neuromuscular complaints. He was treated with an ablative dose of ^{131} iodine. He was seen again three months after discharge and reported that his weight had been increasing, his bowel movements had become normal, and he had no further episodes of muscular weakness or paralysis. Because of subsequent laboratory evidence of hypothyroidism, he was placed on 100 micrograms of levothyroxin daily without further problems.

Discussion

The initial clinical impression in our patient was hypokalemic paralysis secondary to intestinal losses from HIV or HAART associated enteropathy. However, the hypokalemia seemed disproportionate to his modest intestinal symptoms, and further investigation led to the diagnosis of TPP.

Thyrotoxic periodic paralysis, sometimes referred to as hypokalemic thyrotoxic periodic paralysis, is an uncommon but well described complication of hyperthyroidism[1] particularly among young Asian males.[2,3] More recently, TPP has also been described in the United States in Asians, Caucasians, Blacks, Hispanics, and American Indians.[4,5] The clinical manifestations of TPP resemble Familial Periodic Paralysis (FPP).[2,3] Physicians in Western countries may be less familiar with TPP, and the hypokalemic paralysis is often attributed to FPP or one of the numerous other causes of potassium loss via the kidney or intestinal tract.

Although hyperthyroidism is more frequent in females, TPP occurs primarily in young Asian males.[2,3,5] Among 1,366 Southern Chinese patients with thyrotoxicosis 1,188 were females and 178 were males; 25 (1.8%) patients had TPP, of whom 23 were males.[2] Of 19 TPP patients reported in California, all were male between 20 and 44 years of age (mean 31 years).[5] Among the different causes of hyperthyroidism, Graves' disease is most commonly associated with TPP.[2,3,5] The clinical features of FPP are similar but distinguishable from TPP. Both diseases cause sudden transient episodes of painless weakness, primarily involving the proximal limb muscles, which ascends from the legs to the upper body.[2,3,5] Deep tendon reflexes are often decreased or absent. Sensation and consciousness are normal. Ocular, bulbar, and respiratory muscle strength are usually intact. Prodromal symptoms include muscle aches, muscle cramps, and muscle stiffness. Precipitating factors of paralysis include high carbohydrate meals, strenuous exercise, trauma, and infection. Most patients have attacks in the late night or early morning hours and the attacks usually last 1-96 hours.[2,3] The symptoms of hyperthyroidism may precede TPP by 8-24 weeks (average 14 weeks) and many may have had prior transient episodes of weakness.[5] In a series of 45 Chinese patients with TPP[3] the mean plasma potassium on admission was 2.17 +/- 0.08 mmol/l (range 1.1 - 3.5). No patient had a positive family history of TPP, and only 28.9% had a known history of thyrotoxicosis before their first presentation with periodic paralysis. Twenty-seven (60%) had clinical evidence of thyrotoxicosis. Although all were biochemically thyrotoxic, 11.4% had only a mild degree of thyrotoxicosis.[3]

The pathogenesis of TPP is not completely understood. In both TPP and FPP, the hypokalemic periodic paralysis is due to a transient shift of potassium from the extracellular to the intracellular spaces; there is no deficit in total body potassium. The increased frequency in Chinese and other Asian males is unclear, but genetic differences have been found in southern Chinese men with TPP.[6] TPP usually resolves spontaneously but may be complicated by respiratory paralysis. Potassium supplementation has been advocated but can cause subsequent rebound hyperkalemia; therefore, potassium supplementation should be less than 10 mmol/hr unless there are cardiopulmonary complications.[7] In acute episodes of TPP, propanolol therapy alone has been effective without subsequent rebound hyperkalemia.[8]

Autoimmune thyroid disease, particularly Graves' disease, has been described as a late complication of immune reconstitution in patients with advanced HIV disease following HAART.[9-12] Jubault et al[9] reviewed 5 patients who developed Graves' disease while on HAART for HIV infection and compared them with 55 patients on HAART without Graves' disease. Thyroid specific autoimmunity appeared 14 months (range 9-20 months) after starting HAART in the 5 patients who subsequently were admitted for hyperthyroidism 14-22 months after starting HAART. None had thyroid specific autoimmunity before beginning HAART. Thyroid specific autoimmunity was absent in 55 of their HIV patients with similar degrees of immune reconstitution who did not have Graves disease.[9] Chen et al[12] described 17 patients, mostly Black females, with advanced HIV infection who developed autoimmune thyroid disease (AITD) as a late (median 17 months after starting therapy) manifestation of HAART-induced immune reconstitution. Fifteen patients had Graves' disease. The patients with AITD were more likely than controls to be severely compromised at baseline and to experience greater CD4 increments following HAART.

As occurred in the team's patient, the symptoms of thyrotoxicosis such as weight loss, and increased bowel movements, can be confused with complications of HIV infection or adverse effects of HAART.[12] The patient's Graves' disease was probably a late autoimmune manifestation of immune reconstitution following HAART. The unusual complication of hypokalemic thyrotoxic periodic paralysis in this patient is, to the team's knowledge, the first description of TTP associated with HIV infection and immune reconstitution. The incidence of HIV associated TPP may increase as the prevalence of HIV infection increases in Asian populations and HAART becomes more available to these patients.

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Eosinophilic Fasciitis in a 57-Year-old Japanese-American Woman

Deryll U. Ambrocio MD and Kristine Uramoto MD

Abstract

Eosinophilic fasciitis (EF) is a rare connective tissue disorder characterized by symmetrical sclerodermatous skin changes primarily affecting the extremities and histologically, by thickening of the fascia with chronic inflammatory infiltrate containing eosinophils.[1,2] EF is associated with peripheral eosinophilia, hypergammaglobulinemia, and an elevated ESR.[3] Reported is a case of EF in a 57-year-old Japanese-American woman who refused treatment with prednisone, review of other treatment options, and discussion of key differences between this disease and scleroderma.

Introduction

Eosinophilic fasciitis (EF), first described by Shulman in 1974 as a syndrome consisting of diffuse fasciitis, hyperglobulinemia, and eosinophilia,[4] belongs to a diverse group of chronic, systemic, or localized fibrosing disorders, of which, the prototype is systemic sclerosis or scleroderma.[5] It has been suggested that EF is a variant of scleroderma; however, others maintain that it is a distinct syndrome.

Although the etiology of EF is unclear, numerous speculations exist regarding its pathophysiology. In some cases, organic solvents which are known to be autoimmune disease-inducers such as trichloroethylene and L-tryptophan[7,8] have been implicated. Other theories suggest a causal relationship with physical exertion[9] and infection implicating *Borrelia burgdorferi*.[11] There is one case report of EF induced by simvastatin, a cholesterol-reducing agent.[10]

Clinically, the disease usually presents in young adults or middle-age individuals but reportedly has occurred in both children and the elderly. Cutaneous manifestations in EF evolve through three stages; first, there is the edematous diffuse phase followed by the peau d'orange phase characterized by dimpling of the affected skin, then lastly evolving into induration and tightness.[6] The general thinking is that while extremity involvement is common, hand and feet are often spared.[7] However, as Lakhanpal et al. describe in a series of 52 cases of EF, virtually any part of the body may be affected (Table 1). Furthermore, various stages of cutaneous changes may be seen simultaneously in different areas of the body.[3]

The primary presenting symptoms are cutaneous but extracutaneous manifestations including arthritis, synovitis, carpal tunnel syndrome, and associated hematologic diseases have been described. Localized morphea was present in 29% of the 52 cases.[3] Neurological, renal, pulmonary, cardiac, and gastrointestinal involvement are rare.

Case Report

A 57-year-old woman with history of Grave's disease treated with radioactive iodine, hypertension, and hyperlipidemia presented with a three-month history of progressive lumpy, thickened, and edematous skin over bilateral proximal arms, forearms, and shoulders. Gradually, as her skin became more thickened and indurated, she had developed difficulty clenching both fists with limited range of motion, impairing her daily physical activities. In addition, she complained of bilateral throbbing, numbness, and tingling of her hands and fingers, so severe that she was often awakened by the piercing sensation and discomfort. Furthermore, she had ongoing bilateral knee and ankle arthralgias. Before seeing a rheumatologist, the patient was treated with non-steroidal anti-inflammatory drugs (NSAIDs) for tendonitis of the hands and osteoarthritis of the knees and ankles. No other systemic symptoms were noted and the patient denied any correlation of the joint and skin complaints with strenuous activity, exposure to L-tryptophan, or any other unusual chemicals.

Physical exam revealed severe induration of the skin involving bilateral shoulders, proximal arms, and forearms. Edematous skin with peau d'orange was most prominent over the medial proximal arms. The Groove sign, which is an area marked by linear depression of the skin, was positive over the forearms. The patient was unable to clench her fists, inhibited by pain, stiffness, and flexural contractures. There were no digital ulcers or cyanosis. Bilateral Tinel's sign was positive. She had full range of motion of both knees which were nontender but demonstrated small effusions. The ankles were non-tender, without effusions or deformities, and with full range of motion. The remainder of the physical exam was normal.

Laboratory data revealed platelets of 710 (150-450), 12% eosinophils, ESR 55, CRP 6.1, fasting glucose of 115, HgbA1C 7.2, albumin 3.9, globulin 4.2, albumin/globulin ratio of 0.9, total protein 8.1, Ca

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10.3, normal electrolytes, liver function tests, T4, and total CK. Rheumatologic lab studies showed negative anti-SSA/Ro, anti-Jo-1 Ab, anti-DS DNA, rheumatoid factor, Scl-70 Ab, and Anti-ENA. The patient was referred to a dermatologist for biopsy of the upper extremity changes which demonstrated subcutaneous septal fibrosis and chronic inflammatory cells including lymphocytes, plasma cells, and eosinophils compatible with subcutaneous morphea or eosinophilic fasciitis (Figure 1). Knee, ankle, and wrist X-rays showed mild joint spacing narrowing with hypertrophic changes indicative of early osteoarthritis. We diagnosed the patient with hand tendonitis, osteoarthritis, cutaneous and extracutaneous changes suggestive of EF. Of note, carpal tunnel syndrome has been documented in EF patients by Lakhanpal et al.

The patient refused treatment with prednisone, a drug with side effects she did not tolerate in the remote past. However, she agreed to NSAID treatment and initially was placed on celecoxib 200mg one tablet twice daily. After 10 weeks of medical management on celecoxib, the patient's arthritis and hand tendonitis improved significantly but the upper extremity skin changes persisted. After three months on celecoxib 200mg twice daily, the throbbing pain in her hands and fingers recurred and interrupted her sleep at night. The pain eventually became refractory to celecoxib. Furthermore, there was no improvement in the swelling, induration and thickening of the skin in the affected areas. Since she had severe skin changes and extracutaneous manifestations that did not demonstrate spontaneous recovery after eight months of NSAID treatment, she was once again offered steroids and even immune-modulators but she declined treatment. Upon continued follow-up, skin changes persisted and extracutaneous flare-ups occurred.

Discussion

In this patient, symptoms were classic, developing rapidly and resulting in characteristic flexion contractures likely from sclerosis of subcutaneous tissue and/or associated arthritis. The skin changes evolved through the three stages of edematous, peau d'orange, and induration. In Lakhanpal et al.'s review of 52 patients with EF, extracutaneous manifestations included joint contractures, myositis, arthritis, synovitis of the hands, and carpal tunnel syndrome.[3] Hematologic disorders including thrombocytopenia, myelomonocytic leukemia, chronic lymphocytic leukemia, and myeloproliferative disorder were observed[3] and appear to carry a poor prognosis.[6] In light of such prognosis, some recommend performing bone marrow biopsy in patients with EF to establish myelodysplasia.[12]

Diagnosing EF is made clinically and histopathologically and cannot be excluded in the absence of hypergammaglobulinemia, elevated ESR, and peripheral eosinophilia. The latter can be transient even in the absence of specific treatment, so one cannot dismiss the diagnosis because of normal laboratory findings.[3] Histologically, EF is characterized by a fibrous and inflammatory thickening of subcutaneous septal-fascial-perimysial collagenous scaffold as seen in Figure 1. Eosinophilia may be present on histological examination of the fascia but is not required for diagnosis.[3,6,13]

Although EF shares some clinical and histopathologic findings with scleroderma, there are significant differences between both disorders which are key in diagnosing and identifying EF as a disease entity distinct from scleroderma.[3] Table 2 summarizes these distinguishing features.

In EF, spontaneous remission has been reported; however, most patients require systemic steroids which frequently provide favorable outcome.[5] In the cases reported by Lakhanpal et al., four of the five untreated individuals had spontane-

Table 1.— Distribution of Cutaneous Involvement in Eosinophilic Fasciitis, from Lakhanpal et. al

Distribution of Skin Changes	No. of Patients (n=52)
Extremities	
- Arms and legs only	17
- Arms and legs with hands/feet	26
- Legs only	4
- One leg only	1
- One leg with foot only	1
- Arms and hands only	1
- Arms only	1
- One arm and hand only	1
Abdomen	12
Chest	9
Back	3
Buttocks	3
Face/Neck	3

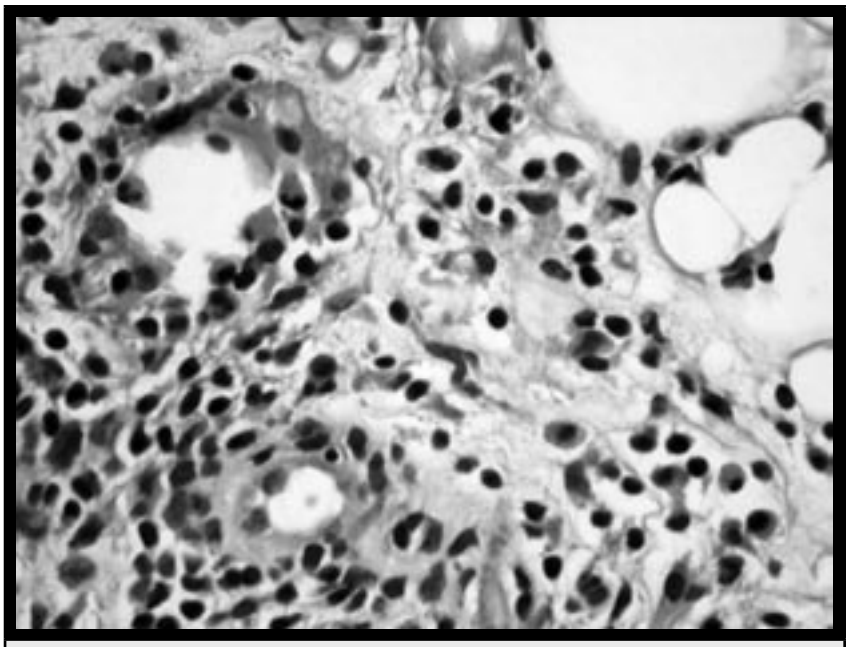

Figure 1.— Skin biopsy, magnified, showing a subcutaneous panniculitis with septal fibrosis, chronic inflammation, including plasma cells, lymphocytes, and eosinophils.

Table 2.— Distinguishing Features of EF and Scleroderma from Lakhanpal et al.		
Features	**Eosinophilic Fasciitis**	**Scleroderma**
Sex	Equal or more common in males	More common in females
Onset with physical exertion	May be present	No known relationship
Involvement of hand	Less common	Unusual (almost 100%)
Raynaud phenomenon	Uncommon	Present
Telangiectases	Uncommon	Common
Digital ulcers	Absent	May be present
Visceral involvement	Uncommon	Common
Hypereosinophilia in blood	Common	Uncommon
Hypergammaglobulinemia	Usual	Unusual
Elevated ESR	Usual	Less common
ANA	Uncommon	Usual
Associated hematologic disorders	May be present	No known relationship
Course	Usually benign	Decreased life expectancy
Nail-fold capillary microscopy	Normal	Abnormal
Skin histology	Epidermis and dermis usually spared	Epidermal atrophy with dermal thickening and fibrosis
Fascial histology	Inflammation	Normal

ous improvement with resolution in two while 59% of cases had a satisfactory response to prednisone alone as compared to treatment with hydroxychloroquine.[3] Treatment with the latter showed satisfactory improvement in 62.5%.

Nonresponders and those patients in whom treatment with steroids is a contraindication have been treated with other drugs including cyclosporine, methotrexate, D-penicillamine, chloroquine, cimetidine, colchicine, azathioprine, and ketotifen, with variable results.[3] Most recently, there has been some promise in the treatment of patients with EF using extracorporeal photochemotherapy (ECP) using UVA radiation.[2]

The clinical course and response to treatment of eosinophilic fasciitis are both highly variable. Although generally thought of as a cortisone-responsive disease, such therapy may be ineffective or effective only at high doses which are accompanied by numerous side effects. Although there have been multiple case reports and studies indicating some type of improvement with the medications described alone or in combination, the fact that the disease may remit spontaneously when untreated questions the validity of the efficacy of any treatment modality.[6]

This team has yet to see what happens to the patient, long term as the standard of treatment for EF has not been validated scientifically nor is there any consensus regarding treatment. While watchful waiting appears to be a reasonable approach to managing those with EF, the use of immunosuppressive agents may be appropriate in the presence of severe inflammation and extracutaneous manifestation such as synovitis, which is often associated with pain and functional limitation. When synovitis is left untreated, it may potentially result in joint destruction.

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Successful Treatment and Limb Salvage of Mucor Necrotizing Fasciitis After Kidney Transplantation with Posaconazole

Abigail S. Harada MD and William Lau MD

Abstract

This is a case of mucormycosis complicated by necrotizing fasciitis in a renal transplant recipient on immunosuppressive therapy treated with posaconazole. Mucormycosis occurs most commonly as an opportunistic infection in the immunocompromised host. This patient, with predisposing risk factors for infection, including diabetes mellitus status post cadaveric renal transplantation on immunosuppressive therapy, is the first reported case of successful treatment of Mucor involving an extremity which was neither fatal nor required extremity amputation.

Introduction

Opportunistic fungal infections have increased in importance due to the growing number of immunocompromised patients and increased use and intensity of immunosuppressive agents. In addition to *Candida* and *Aspergillus*, fungi of the order Mucorales have become increasingly prevalent in immunocompromised patients.[1] Mucormycosis includes all diseases caused by the organisms in the order Mucorales and the family Mucoraceae: *Mucor*, *Rhizopus*, *Absidia*, and *Rhizomucor*.[2] These ubiquitous organisms exist in the environment, soil, manure, plants, decaying material, air, and are known contaminants of laboratory equipment.[3] Mucormycosis is significant for its high mortality rate. Overall mortality is 75-80%, and the mortality rate of disseminated mucormycosis exceeds 95%.[1] This case describes the successful treatment of an immunosuppressed renal transplant recipient with necrotizing mucormycosis of the lower extremity with unprecedented limb salvage at the time of this infection.

Posaconazole was sponsored by Schering-Plough.

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Presentation of Case

A 54-year-old Asian man with a history of diabetes mellitus type 2, end-stage renal disease, status-post cadaveric renal transplantation on immunosuppressive therapy, was admitted to a local hospital for fever, chills, and a painful lesion of the left lateral leg, which progressed to a necrotic ulceration. There was no history of recent travel, trauma, insect bite, or exposure to irritant, allergic, or sick contacts. On initial admission, debridement was performed and biopsy and culture were obtained. The patient was started empirically on cefazolin. He was initially continued on immunosuppressive therapy at previous doses. Oral hypoglycemics were held and the patient was placed on an insulin regimen. Pathology of the tissue debrided from the wound on initial admission revealed acute necrotizing inflammation of the skin and deep subcutaneous tissues. Periodic-acid Schiff stain was positive for short obtuse-angle non-septate fungal elements consistent with Mucormycosis (Figure 1 and 2). Tissue culture ultimately grew *Escherichia coli* and *Mucor.*

After initial identification of fungal infection on hospital day 4, fluconazole (100mg IV qday) was added to empiric cefazolin. On hospital day 6, fluconazole was discontinued and voriconazole (200mg IV bid) was started. The patient underwent 2 additional debridements. On hospital day 14, a 14-day course of amphotericin B lipid complex (450 mg IV qday) was started because of progression of the left lower extremity necrosis. The patient tolerated the amphotericin B lipid complex poorly even after pretreatment with diphenhydramine, acetaminophen, and meperidine. He was subsequently transferred on hospital day 28 to the Kuakini Medical Center for supervision and administration of posaconazole for his mucormycosis infection.

Examination at time of transfer revealed the patient was hemodynamically stable with a low-grade fever. The anterolateral left leg showed multiple deep necrotic ulcers with pale avascular centers and surrounding hemorrhagic borders (Figure 3). There was prominent erythema, edema and induration of the perilesional skin. No undermined borders, greenish discoloration, or purulent drainage was appreciated. No regional lymphadenopathy was noted. Neurologic examination was significant for hypoesthesia of the lower extremities. The lung, heart, and abdominal exams were normal.

At transfer, the patient had a persistent leukocytosis (white blood cell count 11,000, 93% neutrophils and 3% bands), BUN 39 and creatinine 4.3, and remained symptomatic with fever and chills. He was resumed on hemodialysis for his deteriorating renal function and was tapered off immunosuppressive therapy in light of his progressive infection. Wound culture at transfer grew *Escherichia coli* and *Alcaligenes* species sensitive to piperacillin-tazobactam. At time of transfer, amphotericin B lipid complex and cefazolin were discontinued and patient was initiated on piperacillin-tazobactam (2.25 mg IV q8hr) for 24 days and posaconazole at 400mg po bid. Blood cultures taken on repeated occasions were negative throughout both hospitalizations.

Due to the persistence of necrotic tissue despite multiple debridements, the patient underwent 2 additional wide excision debridements (total hospital day 51 and 73) in preparation for skin graft. Involvement of the posterolateral aspect of the deep muscle compartment and fascia were observed. Histology of specimens taken from each procedure both revealed dermal necrosis and inflammation with staining negative for fungal organisms. On hospital day 96, split-thickness skin graft from the right and left anterior thigh to the left lower extremity was performed which ultimately had an 80-90% take. The patient defervesced and white blood cell count normalized to 6,000 without bandemia.

Hospital course was complicated by non-Q wave myocardial infarction for which the patient underwent percutaneous transluminal coronary angioplasty with stent placement. The patient also had an episode of upper gastrointestinal bleeding and a subsequent non-Q wave MI. Once the patient was stabilized, endoscopy was performed which revealed a gastric ulcer with biopsies negative for *Helicobacter pylori*.

On hospital day 128, the patient was discharged home. At that time, he was able to bear weight and ambulate with assistance. Hemodialysis and physical therapy were continued as an outpatient and the patient was maintained on the same dosage of oral posaconazole for one month post-discharge. Approximately, a year and a half later, the patient died of septicemia from bacterial gangrene of his extremities. He ultimately had both lower extremities amputated a few weeks prior to his demise. There was, however, no evidence of Mucor at the time of his death.

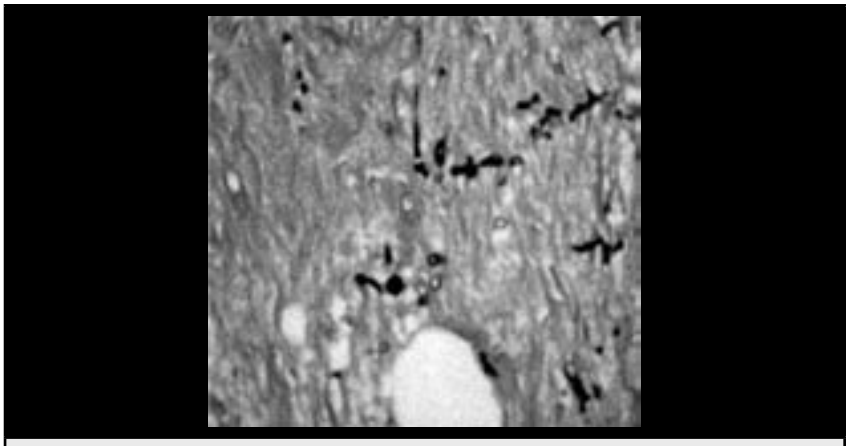

Figure 1.— (Periodic-acid Schiff stain revealed short obtuse-angle non-septate fungal elements consistent with Mucormycosis)

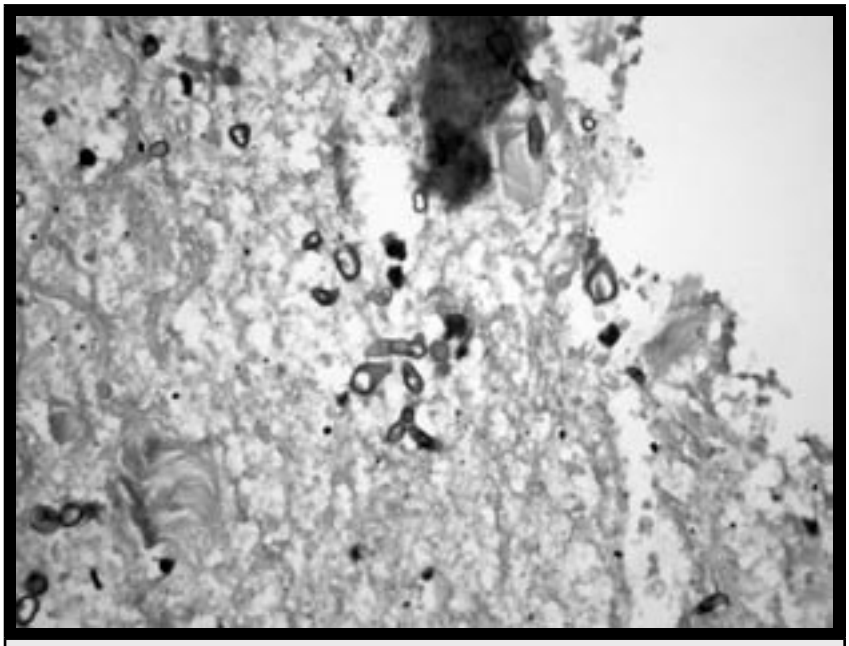

Figure 2.— (Periodic-acid Schiff stain revealed short obtuse-angle non-septate fungal elements consistent with Mucormycosis)

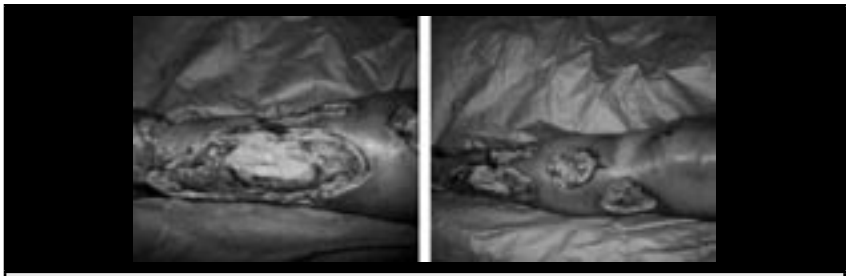

Figure 3.— (Multiple necrotic ulcers with avascular centers and surrounding hemorrhagic borders extending to the muscle)

Discussion

Mucorales belongs to the class Zygomycetes. This class of fungi is characterized by production of aseptate hyphae and sexual production via the formation of zygospores. The order Mucorales is made up of species from the genera *Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Saksenaea, Syncephalastrum, Cunninghamella,* and *Cokeromyces*. Mucormycosis includes all diseases caused by these organisms, and is characterized by angioinvasive disease in immunocompromised hosts.[4]

Mucormycosis has clinical manifestations including rhinocerebral, pulmonary, gastrointestinal, central nervous system, disseminated, and cutaneous disease. Rhinocerebral and pulmonary mucormycosis are the most common presentations

of this fungal infection representing aerogenous pathogens.[3] The infection begins in the palate or nasal sinuses and disseminates to adjacent bone, sinus, orbit, and brain. Pulmonary mucormycosis is a rapidly progressive necrotizing and hemorrhagic pneumonia.[5] Infection occurs exclusively in immunocompromised hosts. Predisposing conditions include transplant recipients on immunosuppressive therapy, acquired immunodeficiency syndrome (AIDS), cancer patients receiving chemotherapy, burn patients, diabetes mellitus (especially in the setting of ketoacidosis), leukemia and lymphoma, renal failure patients, recipients of chronic antibiotic or steroid therapy, traumatic wounds, and complicated postoperative courses.[3,6]

Cutaneous mucormycosis represents less than 10% of reported cases. Primary disease often occurs in patients with disrupted cutaneous barriers, as a result of either traumatic implantation of soil, maceration of skin by a moist surface, or even via direct access through intravenous catheters or subcutaneous injections where fungal spores present on skin are believed to directly inoculate tissue.[7] Cutaneous infection spreads rapidly as spores germinate into invasive hyphae that disseminate deeply to underlying fat, muscle, fascia, and even bone.[6] Secondary cutaneous mucormycosis may occur via hematogenous spread from a preexisting noncutaneous infection in another organ system.[3]

There are two clinical variants of cutaneous mucormycosis, a subacute "superficial" form and a "gangrenous" form. The "superficial" variant is characterized by vesicles and pustules that ulcerate and form eschars. Patients typically recover with conservative debridement and intravenous amphotericin B. As exemplified by our patient, the "superficial" variant may progress to the more invasive "gangrenous" mucormycosis in immunocompromised hosts.[3] Our patient had multiple predisposing risk factors including diabetes, renal transplant with acute rejection, and high dose steroid and immunosuppressive therapy. It resembles necrotizing fasciitis and has a mortality approaching 80%.[7] This unique angiophilic infection is characterized by infectious vasculitis, vascular occlusion, infarction, and ischemia or hemorrhage.[8] The clinical appearance however, is nonspecific and may be misdiagnosed as *Pseudomonas*, *Aspergillus*, *Histoplasma*, *Cryptococcus*, *Aeromonas hydrophila*, vasculitis, pyoderma gangrenosum, and other necrotizing infections.[3]

Mucorales are found throughout the natural world and organisms have been cultured from the skin, nasal passages, stool, and oral cavities of healthy individuals.[3] Full-thickness skin biopsy and culture are diagnostic of cutaneous disease.[9] Fungi of the order Mucorales histologically appear as irregularly shaped, broad (6-25 μm in diameter), non-septate hyphae with right-angle branching. They are rarely mistaken for *Aspergillus* or other Hyalohyphomycetes, as these fungi have septate hyphae with dichotomous branching at sharp angles. Hyphal infiltrations are often found near blood vessels in the organ of primary infection and in the area of septic thromboembolization in the terminal vascular bed of other organs if dissemination has occurred.[1]

Mucormycosis is an increasingly common infection in immunocompromised patients. As the incidence of diabetes and cancer rises in the increasingly obese and elderly United States population, so does the reported cases of mucormycosis.[7] Successful treatment of mucormycosis involves correction of the underlying predisposing condition or improvement of immunosuppression, debridement, and if needed, extensive surgical resection of the necrotic tissue, and medical treatment with antimycotic agents.[1] Early diagnosis is also important because small, focal lesions can often be surgically excised before they progress to involve critical structures or disseminate. Unfortunately, there are no serologic of PCR-based tests to allow rapid diagnosis. Thus, it is essential to maintain a high index of clinical suspicion and to pursue a diagnostic biopsy.[7]

Mucormycosis is often rapidly progressive, and antifungal therapy alone is insufficient to control the infection. Surgery is often urgently necessary due to the significant amount of tissue necrosis with resultant poor penetration of anti-fungals to the site of infection. Differing strains of mucormycosis have broad susceptibilities to antifungal agents; some strains may be highly resistant to amphotericin B. Therefore, the recommended dose of amphotericin B deoxycholate has been 1-1.5 mg/kg/day, which leads to high toxicity rates. The lipid formulations of amphotericin are less nephrotoxic and may be given at higher doses for extended periods of time, albeit at an increased cost. Currently, the available pharmacokinetic data, animal model data, and retrospective clinical data all support the first-line use of high dose liposomal amphotericin B for mucormycosis, with amphotericin B lipid complex as a second-line agent.[7]

Caspofungin, the first member of the echinocandin class of antifungal drugs available in the United States, has been shown to have minimal activity against the agents of mucormycosis when tested in vitro by standard techniques. In addition, clinical experience with caspofungin in the treatment of mucormycosis is extremely limited and more studies investigating the role of echinocandins in this area are needed.[7]

Hyperbaric oxygen has been used as adjunctive therapy, but its role has not yet been determined.[10] One theory regarding its utility is that higher oxygen pressure improves the ability of neutrophils to kill the organism. Also, high oxygen pressure is found to inhibit the germination of fungal spores and growth of mycelia in vitro. Unfortunately, however, controlled clinical trials regarding outcomes of patients treated with hyperbaric oxygen are not available.[7]

Azole therapy was initially started in our patient due to concern for preservation of renal function and the lack of significant improvement in his clinical status. Addition of the less toxic formulation, amphotericin B lipid complex, with reduction of immunosuppressive therapy and conservative debridement had proved to be ineffective in controlling the infection. Until recently, itraconazole was the only marketed azole drug that was shown to have in vitro activity against Mucorales.[7] Posaconazole is a new extended-spectrum azole antifungal on the market that has demonstrated both in vitro and in vivo activity against Mucorales.[11] Reduction of immunosuppression, strict glycemic control, multiple wide excision debridements, addition of a new azole, posaconazole and delayed reconstruction resulted in successful eradication of the infection with salvage of the limb. The success of posaconazole in this case of mucormycosis supports that seen in other patients treated with posaconazole as salvage therapy for refractory mucormycosis.[11] Success rates of up to 60% have been described in patients who had failed or were intolerant of standard therapy, particularly lipid formulation amphotericin B.[12,13] Further data are needed to determine whether posaconazole, alone or in combination with amphotericin, may be useful for the initial treatment of mucormycosis.[7]

To the authors' knowledge, this is the first reported case of infection by Mucor involving the extremity of a chronically immunosuppressed diabetic renal transplant recipient which neither required amputation nor was fatal. Although randomized studies regarding the most efficacious antimycotic treatment of mucormycosis are lacking, prompt diagnosis, reversal of predisposing conditions, and combined surgical and medical antifungal chemotherapeutic approach to treatment remains the standard of care the treatment of this often fatal disease.[3]

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Standards and Guidelines for Willed Body Donations at the John A. Burns School of Medicine, 2007

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Introduction

Numerous abuses have been publicized across the country concerning the unethical and often illegal trafficking of human body donations used in unauthorized activities. The advent of new preservation techniques, such as plastination, renders human material indestructible and available for display also raising numerous ethical concerns such as placement in controversial display venues as well as eventual disposition.[1] These objectionable activities have prompted various medical schools and health care organizations to establish ethical standards and guidelines for the use of human anatomical donations. Most notably, the University of California undertook an 18-month comprehensive review and organized a system-wide advisory board that established guidelines for public review, http://www.ucop.edu/ucophome/coordrev/policy/PP110305standards&guidelines.pdf. At the same time, national organizations, including the American Association of Anatomists (AAA) and the American Association of Clinical Anatomists (AACA), are crafting language that stipulates the ethical use of human anatomical material in an attempt to establish best practice guidelines for ethical and professional use of anatomical remains.

The John A. Burns School of Medicine (JABSOM) utilizes human cadaveric material for medical research and teaching activities.[2] The Willed Body Donation Program (WBDP) is responsible for accepting and administering donations. JABSOM relies heavily on the generous support of altruistic community members for the implementation of the WBDP without whose donations would severely hamper research and educational programs.

Anatomical dissection is an essential learning experience for medical students, residents, and allied medical professionals. Use of the anatomical donations is dynamic and varied facilitating a wide range of basic medical research and clinical education experiences such as gross anatomical dissection, pathology instruction, prosthetic device development, surgical technique improvements, technical evaluation of medical imaging devices, and many other activities. Remains received by WBDP are also used in various continuing medical education workshops involving clinicians, allied health practitioners, and mortuary science education.

The Uniformed Anatomical Gift Act of 1987 established JABSOM as the health center for the collection and preparation of donated human remains. Annually, approximately 50 people donate their bodies providing an extraordinary gift to the university that is central to the JABSOM mission. The WBDP is dedicated to the ethical and respectful treatment in the storage, use, and disposition of all human material. The WBDP has established standards and guidelines applied to anatomical materials donated to the University for use in non-clinical research and education endeavors, i.e., non-patient care activities such as transplantation or clinical therapy. These standards and guidelines are based primarily on the guidelines stipulated by the University of California, and currently in discussion by the American Associate of Anatomists and the American Association of Clinical Anatomists.

Use of Human Anatomical Material

Anatomical materials are utilized immediately as fresh tissue, or preserved for use at a later date by means of freezing or as specially preserved tissue for use in anatomical preparations that include dissections. Plastinated and skeletal material is also prepared and used for educational purposes. As a priority JABSOM supports appropriate use of anatomical materials by faculty, students, and residents. In addition, researchers on the Kaka'ako campus, qualified non-UH researchers, affiliated and nonaffiliated educational institutions located in Hawai'i, and certified continuing medical education programs and workshops also incorporate anatomical materials into educational efforts. The priority for specimen allocation is: 1) University of Hawai'i students and researchers at JABSOM; 2) Students and researchers at other University of Hawai'i campuses on O'ahu; 3) External non-commercial research and education organizations; 4) Healthcare Industry-sponsored educational and training programs only at the Kaka'ako medical sciences complex.

The University has established a defined reporting structure for responsible oversight of the WBDP. The Director of the WBDP is responsible for maintaining the anatomy laboratory, enforcing rules associated with anatomical material and is the representative of the program in the community. The Director is responsible for the daily operation of the Program and reports directly to the Responsible Executive Officer (REO). The REO is Professor and Chair of the Department of Anatomy, Biochemistry and Physiology, and is responsible for operation of the WBDP and approving usage of the cadavers. An Anatomical Materials Review Committee (AMRC) consists of the REO who serves as Chair, the WBDP Director, and a member designated by the Dean of JABSOM. The AMRC recommends guidelines, policies, and procedures for cadaveric usage.

Acquisition and Administration of Donated Materials

A critical component of a WBDP is the ethical acquisition and caretaking of donated anatomical material. Only approved informed consent forms and other supporting documentation for membership in the WBDP is used for this purpose. A spouse, registered domestic partner, or other individual may initiate the donation of anatomical remains on behalf of the deceased. Such donations are governed by applicable state statutes or applicable power of attorney regula-

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tions. Only upon approval by the Director are third party donations accepted following the completion of required documentation. Unclaimed bodies are not accepted by the WBDP since health records are unavailable. All donors have the right to specify the return of their cremated remains. The Director manages and tracks all aspects of donation, including anatomical preparation, handling, inventory management, allocation, and disposal of anatomical materials. The Director also makes available to the REO, members of the AMRC, and the Dean of the School of Medicine, information that pertain to anatomical preparation, cadaver log books, and inventory management. The Director makes available the records for all cadavers utilized for the WBDP, all cancelled memberships, and all current cadavers in the WBDP. The Director also provides all anatomical use requests, contracts, and budgets for all courses through the WBDP at JABSOM.

A critical component to the WBDP at JABSOM is the guarantee that all donated material is tracked throughout the duration of its use. Management of the cadavers follows basic tracking guidelines. Upon receipt, all cadavers are entered into the cadaver logbook and assigned a unique identification number. Until the time of cremation, all references to the cadaver are performed using the identification number system. Pre-registration for donors is required, but when registration for some reason is not possible, cadaveric preparation is not performed until all postmortem documents are signed by the next-of-kin. It is the Director's decision as to whether a cadaver is to be embalmed or used as fresh (unembalmed) material. All unembalmed cadavers are tested for infectious diseases including but not limited to HIV, Hepatitis B, and Hepatitis C. Reactive anatomical material is not accepted for use at JABSOM. Cadavers testing positive for HIV, Hepatitis B, or Hepatitis C are cremated as soon as all permits are obtained.

All portions of a cadaver are retained if the donor form specifies remains are to be returned to the next-of-kin. In this case, all portions of that cadaver are assigned a unique cadaver number physically attached to the material. Cadaver tissues are stored until time of cremation. All records, logs, and storage locations are made available to the REO, members of the AMRC, the Dean of the School of Medicine, or anyone else approved by a member of the AMRC. However, donor anonymity is maintained to protect WBDP participants.

The REO conducts unannounced inspections of the anatomy lab, the morgue, the plastination lab, or any location where cadaveric material is present to verify full compliance. Inadequacies are brought to the attention of the Director. The Director establishes a schedule for physical inventory of donated anatomical materials on an annual basis or more frequently if necessary. In addition, unscheduled audits are conducted to verify fiscal management and management of donated materials.

JABSOM funds the administration of the WBDP by assessing costs to all users of anatomical materials. A preparation fee is based on a master charge description that corresponds to the national rate. A charge is levied in accordance with UH Standard Operating Procedures. Additional fees for use of anatomical materials comply with University policies on recovery of indirect costs.

Physical security of all cadaveric material is insured by numerous safety mechanisms. To ensure that donated materials are protected from misuse, only personnel approved by the AMRC are authorized access. Physical security mechanisms at the Kaka'ako complex employ multiple levels including individualized coded card-key entry access, alarm systems, card-key access, surveillance cameras, and 24-hour security guards.

Requests and Distribution of Cadaveric Material

The WBDP insures that anatomical donations are not distributed or used in any unethical or illegal fashion. Numerous safeguards have been established: Only anatomical material originating from JABSOM can be used in the anatomy laboratories. Anatomical material from other sources are never accepted. Under no circumstances does anatomical material leave the State of Hawai'i. All material is accompanied by proper documentation, and is under the direct supervision of the Director and REO during transportation. All requests for use of donated anatomical materials include appropriately detailed descriptions of the proposed use, the research protocol, appropriate bio-safety approvals, the teaching or training application, and the expected duration of the programmatic use. The Director and the REO with general guidance from the AMRC render all decisions concerning allocation. JABSOM remains custodian of all donated material and by policy, donations are never assigned to third-party brokers or intermediaries. Anatomical materials may be transferred directly from JABSOM as the provider to an approved end-user for purposes of teaching or research. All end-user facilities that request and receive anatomical materials must have prior approval by the WBPD and undergo routine inspection by the Director or his/her designee. An individual or entity approved for a loan of anatomical materials must certify their purpose and agree to terms, duration of use, and conditions for return to JABSOM. The WBDP maintains permanent teaching collections, such as skeletal or plastinated specimens, utilizing anatomical material only from those donors who do not request return of cremains.

Anatomical Material Return and Disposition

Appropriate disposition of anatomical materials occurs through cremation and scattering at sea, or by other legal methods of disposition according to the Hawaiian Health and Safety Code. In exceptional cases, the REO may approve alternate disposition arrangements but only if indicated by the donor at the time of donation.

The WBDP records returns of cremains and final disposition of cadavers. These documents are retained in the individual donor files. Small materials are not individually catalogued by the WBDP including microscopic tissue samples, bodily fluids, teeth, and specimens preserved in paraffin blocks or as tissue slides, and other small tissue components. In general, these materials are defined under separate criteria by the Hawaiian Health and Safety Code, and are disposed in accordance with Code standards.

An annual memorial service is held with invitations extended to donor families. This activity is organized and implemented by the medical students and serves as a tribute to the donors and their families for making such a critical contribution to the education of health care workers in our community.

Program Staffing and Work Areas

An important aspect of an ethical WBDP is a unit staffed by caring, empathetic professionals who clearly understand the critical role of human anatomical donation in achieving the mission of JABSOM.

Program employees are subject to University personnel policies, including those on hiring and periodic performance evaluation. All employees are subject to a completed background check. Faculty and staff involved in the WBDP receive institutional training in blood borne pathogens and chemical safety. Work areas include laboratories appropriately designed for anatomical preparation, cadaveric dissection, storage of frozen and embalmed material, and administration of the program.

Conclusion

Recently, a disturbing trend has developed nationally, driven by unscrupulous third party brokers who use hotels or other public venues for so-called anatomical training exercises, and expose the workers and subsequent parties to chemical or bio-hazardous materials. Many of these venues do not comply with state and federal regulations governing biological, pathological, and chemical laboratory requirements. Worse still are those individuals motivated by greed and who engage in the illegal trafficking of human body parts. JABSOM is very concerned about the unethical and illegal use of anatomical material which impacts negatively on our community health. The Hawai'i public can be assured that through the WBDP, JABSOM upholds the hallowed tradition of cadaveric dissection and is committed to a code of ethics that are based on informed consent and a transparent administrative system.

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Ocean Science, Genomics, and Pharmaceutical Discovery

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Many of the drugs used in daily clinical practice in the fields of cancer chemotherapy and antiinfectives are natural products or have been developed from natural products leads. Most of these discoveries were made from plants, fungi, or bacteria: paclitaxel, irinotecan, adriamycin, penicillin, erythromycin, the aminoglycosides, etc. These compounds were discovered in the 1960s and 70s and ever since then the pace of introduction of new drugs derived from natural products has decreased. The reasons for this are many and varied. One of the most important is that the rate of discovery of truly new natural products has slowed dramatically. It has been estimated that in some industrial natural product screening programs the rediscovery rate is above 95%.

That is, the compounds that are found are closely related to already known compounds, do not offer new biological activities, and have only minimal potential for the protection of intellectual property.

One of the reasons for this development is that the biological diversity of the source organisms being used is limited, as in the case of the Streptomycetes, the workhorses of the pharmaceutical industry in the 1960s and 70s. In the case of higher plants, their diversity has been explored to the limit, as roughly 95% of all existing plant species have been described. It is therefore unlikely that new plant families with entirely new chemistry will be discovered.

The situation with microorganisms is distinctly different. The genomics revolution has provided scientists with the tools to estimate biological diversity in a sample without having to culture the microorganisms, the technique science has relied on for more than 100 years to enumerate and characterize bacteria and fungi. Bacteria can now be enumerated and identified on the basis of their characteristic DNA sequences that can be accessed through polymerase chain reaction (PCR). These molecular techniques allow scientists to estimate that less than 1% of all bacteria present in a soil or water sample have been cultivated in the laboratory. For samples from environments rich in nutrients, such as soil, the percentage is highest, whereas for water samples the percentage of microbes brought successfully into laboratory culture is the lowest. In fact, until ten years ago it was not even known that open ocean waters were teeming with microorganisms. In addition, Craig Venter and his coworkers have shown that the microbial diversity in the ocean changes dramatically with geographic location. It is no exaggeration to state that scientists have at best just scratched the surface of the microbial biological diversity in the ocean.

These developments in molecular biology tell scientists that all of the pharmaceutically useful compounds from microorganisms have been obtained from a very small subset of all existing microbes. This realization sets the agenda for a new push for the discovery of natural products with pharmacologically valuable properties: more of the existing biological diversity of potential producer organisms that is presently not represented in culture collections must be sampled. If scientists succeed in expanding the range of cultivatable organisms by a factor of five or ten, they may expect a bounty of new compounds, enzymes and processes. It is known that the organisms are "out there", scientists just need to invent the tools to harness this untapped diversity.

Three different approaches are being pursued. The first attempts to industrialize the cultivation of microorganisms by rendering it massively parallel. In this approach one attempts to separate fast growing, very often known bacteria, the "weeds", from slow growing ones. This process borrows from concepts first developed in computer science and is heavily automated. It aims to supplant the manpower intensive traditional approach to cultivation in place for the past hundred years with one that in essence makes cultivation a numbers game. The focus of the work is no longer to bring a specific microorganism into culture, but to bring into culture representatives of a broad range of biological diversity present within a given sample.

In the second approach one does not attempt to isolate and cultivate the unknown microorganism itself. Instead one isolates the "community DNA" from all the organisms present in the sample and attempts to express this foreign DNA in a suitable well-behaved, well-understood host, such as *E. coli* or Streptomyces. This approach takes note of the observation that the genes encoding the production of antibiotics and other potentially useful chemicals are clustered in close spatial proximity on the bacterial chromosome. Thus, if one is able to isolate large pieces of DNA from an unknown organism, say 100,000 base pairs (100kB), to introduce these pieces into another bacterium, and to induce the latter to express this foreign DNA, one can get access to the chemical product of gene clusters present somewhere in the DNA of an unknown organism present in a sample without having to isolate and mass culture it. Presently, this approach is in the tool development stage. The feasibility has been demonstrated in a few cases, but there is still sometime until this becomes technology that can really be applied.

The third approach still relies on traditional culture techniques but focuses the biological discovery process on unusual sources and on underexplored taxa. Thus, at University of Hawai'i at Manoa (UH), in the laboratory of the author's colleague Richard Moore a focus on terrestrial blue-green algae and the natural products they produce led to the discovery of an extremely potent antimicrotubule agent, cryptophycin, that has entered the industrial development pipeline as an anticancer agent. Cyanobacteria had not been systematically investigated for the natural products they produce until Professor Moore started this program.

Bill Fenical, a colleague of both the author and Professor Moore at the Scripps Oceanographic Institution, has discovered a very potent proteasome inhibitor that has just entered the clinical development pipeline also as an anticancer agent. A hitherto unknown obligate marine microorganism found in marine sediments produces this compound. In this example it is not the microbiology that was the

hard part, but the recovery of viable biological samples from the ocean floor some several thousand feet below.

Another colleague, Mark Hamann at the University of Mississippi has discovered a group of alkaloids, the manzamines, from a sponge first collected in Indonesian waters. The manzamines are being developed as an antimycobacterial drug. Most interesting for the present discussion is the observation that the producing organism is not the marine invertebrate itself but a bacterium living within the sponge, possibly symbiotically. This as it turns out holds true for several compounds with favorable biological activity profile from marine invertebrates. Another example are the bryostatins, which were first discovered from a bryozoan, *Bugula neritima*, in waters off San Diego and then also off the Carolina coast. This compound is an extremely potent inhibitor of protein kinase C. However, its future as a drug lead was doomed because of its origin from a marine invertebrate that had to be collected in the ocean and had not been cultured. Continued work on the biology of the organism, however, revealed that the producing organism is not the bryozoan itself but a symbiotic, hitherto unknown bacterium. In fact, the bacterium is specifically associated with the larvae of the bryozoan that are released during spawning events. This latest discovery opens up the prospect of producing the bryostatins through fermentation of either the native bacterium or of a heterologous host to which the biosynthetic genes have been transferred in an approach akin to the one discussed earlier.

To the natural products chemist it is apparent from the inspection of chemical structures that many of the compounds isolated from marine invertebrates in the past three decades are in all likelihood produced by microorganisms associated with these invertebrates. The chemical anatomy of such compounds is often reminiscent of structural features and specific biochemical processes we know from microbial natural products. Given the taxonomic distance between invertebrates and microorganisms it seems at a minimum unlikely that these putative biochemical processes should have arisen independently twice during evolution. The example of the laulimalides may be instructive here. These macrolides are potent microtubule poisons with a taxol-like activity. They were discovered at the UH from a sponge collected in the Marshall Islands. Given the chemical structure of laulimalide, the natural products chemist is confident in suggesting that a microorganism related however distantly to Streptomyces will one day be identified as the penultimate producing organism. Until that day, the laulimalides are unlikely to enter clinical development unless chemists can develop through total synthesis an analog that is radically simpler in chemical structure while retaining biological potency and efficacy.

There is an additional example that is worth discussing as it represents a slight twist on this idea of the symbiont. The kahalalides were first discovered at the UH some 15 years ago from a nudibranch in brackish waters off Black Point. Kahalide F, one of the group of structurally related compounds, is in clinical development as an anticancer agent. The animals from which the compound was first obtained feed on an alga that blooms at Black Point in the spring. It was first assumed that the alga was the producing organism until the marine bacterium *Vibrio* that lives attached to the algal surfaces was found to be the producing organism.

This discussion will hopefully have demonstrated to the reader that the ocean is a hitherto underexplored and underappreciated realm of microbial diversity that has come to our attention within the last ten years. As scientists discover and learn how to harness this biological diversity, they will be poised to tap into new chemistry that they have good reason to believe is associated with these new biological source organisms. In turn the new chemistry will provide scientists with drug leads for the treatment of cancer and infectious disease.

There is some exciting technology on the horizon and UH is poised to take advantage of these new developments through its interdisciplinary research programs in oceanography, chemistry, and cancer research. The Pacific Research Center for Marine Biomedicine, jointly funded by the National Institutes of Health and the National Science Foundation, is only one of the manifestations of our desire to shape this research area.

For more information on the Cancer Research Center of Hawai'i, please visit its website a www.crch.org.

Issues in Medical Malpractice IX

S.Y. Tan MD, JD, Professor of Medicine and Adjunct Professor of Law, University of Hawai'i

Question: Doctors most prone to lawsuits:

A. Are ultra-busy practitioners.
B. Have poor interpersonal skills.
C. Talk down to patients.
D. Rarely apologize.
E. Belong in high risk specialties such as neurosurgery and obstetrics.

Answer: All correct. The first four choices speak to arrogance, hasty evaluations, and poor communication skills. They predictably get doctors into trouble. The last option is also correct. Here the reason is the catastrophic and tragic neurological injuries arising out of negligent care at birth or during neurological interventions. This translates into substantial damages for the plaintiff and his/her lawyer.

Communication

What prompts a lawsuit are poor communication and perception that the physician is uncaring and at fault for the bad result. The combination of bad outcome and patient dissatisfaction is a recipe for litigation. On the other hand, quality of medical care correlates poorly with malpractice lawsuits. In a study of obstetricians/gynecologists, the quality of treatment as judged by peer review was not different in frequently-sued versus never-sued doctors.[1] In another study on the relationship between malpractice and patient satisfaction, patients of doctors with prior malpractice claims reported feeling rushed, feeling ignored, receiving inadequate explanations or advice, and spending less time during routine visits when compared to patients of doctors without prior claims.[2] Beckman et al have documented that communication problems exist in over 70% of malpractice cases, with these problems centering on four themes:

1) Deserting the patient;
2) Devaluing patient/family views;
3) Delivering information poorly; and
4) Failing to understand the patient/family perspective.[3]

In a telling study by Lester and Smith, the authors asked 160 adults to view a videotape of a clinical encounter that resulted in complications. In one scenario, the doctor used positive communication behaviors such as eye contact and friendly voice, and in another, negative communication behaviors (e.g., short contact period, unsmiling).[4] They were then asked whether they would be inclined to sue the doctor.

The videotape viewers, as a group, expressed the belief that negative communication behaviors by the physician increased litigious intentions. An increased perception of physician fault for the bad result, as well as uncertainty as to the reason for the bad outcome also raised litigious feelings. These results prompted the authors to state:

> *". . . positive communications would result in less litigiousness because the physician is viewed as having cared about the patient and thus having acted in good faith. In the world of relating, good faith counts for a lot: one's reading of good and bad faith tends to define who is a malicious villain and who is a fallible human being. On the other hand, negative behaviors tend to communicate lack of concern and even antagonism and may be seen by patient as a violation of the unwritten but inherent "caring" nature of the physician-patient relationship. Long before there is any medical outcome to be concerned about, the patient may believe that the physician has already done something "wrong" simply by relating in what is perceived to be an uncaring manner. This may set the stage for later retaliation if something does go wrong."*

The authors' advice:

> *"To lower litigation risk by using extra medical procedures and tests, consultation, and extensive documentation, often known as 'defensive medicine', may miss the point. Defensive medicine is not so much a tool to prevent lawsuits as it is to win them if they do occur. But if the intention is to prevent a lawsuit in the first place, forging a physician-patient bond that can effectively resist the pressure of our litigation-crazed and socially antagonistic society seems indispensable."*

Good advice, indeed. Every effort should be made to communicate effectively, with empathy and tact. And communicating well begins with active listening.

Talking with Patients: Listening actively to patients is a basic function of a good doctor. This means more than attentive listening. The doctor should show his or her understanding of what had just been said by the patient. This reassures the patient that the doctor has heard and understood the questions or concerns. Body language is important too. Experts tell us that 55% of information conveyed in a normal conversation occurs via non-verbal means. The percentage may be even higher in a medical encounter. And being able to explain the condition, procedure, or medication in simple lay terms is critically important. Patients want their doctors to listen to them and to explain their conditions and treatment plans in simple, understandable language. During the course of a good doctor-patient relationship, the physician can effectively reduce the odds of being sued by educating the patient regarding the scope and limitations of medical care, and the patient's own responsibilities in complying with medical advice, medication, and follow-up.

The physician should give patients ample opportunity to tell their story and to ask questions. In a well-publicized study, only 23% of patients were able to complete their opening statement before the doctor interrupted, which occurred, on the average, 18 seconds after the patient began to speak![5]

The doctrine of informed consent is largely based on proper and

timely communication between provider and patient. Specially prepared professional literature often helps to answer the patient's questions. Videotapes and DVDs can help to inform, and are particularly effective in explaining surgical procedures, e.g., cholecystectomy. Nothing, however, can replace the doctor-patient discussion, which should always supplement a brochure or video presentation. Such communication must be carried out at a leisurely pace, way before an elective intervention, and certainly not at the last minute along the waiting corridors of the operating suite. Avoid telling patients that the procedure is very simple, or that there will be no problems. And, of course, never guarantee results.

After obtaining the permission of the patient to avoid violating confidentiality and HIPAA rules, engage family members in the discussion if at all possible. Involving family members facilitates achieving a good clinical outcome. One ought to remember that it is the family who sues if the patient dies or suffers irreversible cognitive injuries.

Do not hesitate to call the patient or family members at home in order to remind, reassure, or clarify. This is especially important if the treatment or test-procedure had lasted longer than usual, was traumatic, complicated, or may result in post-treatment complications. For anything more than the routine, the healthcare professional or assistant should be available after hours to assist with patient concerns. Answer all patient phone calls in a timely fashion. It is usually best to make the call yourself rather than relegate it to an assistant. Patients appreciate a doctor who has taken the time to personally return his/her phone call. It means the doctor cares. And appreciative patients usually do not sue.

Telephone Communication: The four basic rules are:

1) listen and instruct carefully,
2) insist on seeing the patient or have the patient go to the emergency department if there is any doubt,
3) ask the patient (or pharmacist) to repeat your instructions or orders to minimize miscommunication, and
4) document everything in writing. Risk managers warn in particular of calls concerning abdominal or chest pain, high fever, seizures, bleeding, head injury, dyspnea, tight orthopedic casts, visual complaints, and onset of labor.[6]

And practice consultants recommend getting rid of "confusing menus, canned ads, irksome music, assurances that 'your call is important', and waits that border on eternity."[7] Finally, don't forget that a doctor-patient relationship may be formed as a result of a phone conversation, with an attendant legal duty of care.

This article is meant to be educational and does not constitute medical, ethical, or legal advice. It is excerpted from the author's book, *"Medical Malpractice: Understanding the Law, Managing the Risk"* published in 2006 by World Scientific Publishing Co., and available at Amazon.com. You may contact the author, S.Y. Tan MD, JD, at email: siang@hawaii.edu or call (808) 526-9784 for more information.

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March 2007					
3/3	Multi	Hawai'i Chapter of the American College of Physicians	Hawai'i Prince Hotel	Annual Scientific Meeting	Tel: (808) 586-7478 Email: sharonch@hawaii.edu
3/3-3/10	IM, FM	Keck School of Medicine of USC	Mauna Kea Beach Resort, Hawai'i	Diagnostic Skills in Internal Medicine	Tel: (800) 872-1119
3/5-3/9	Multi	St. Francis International Center for Healthcare Ethics	Hawai'i Medical Center -- East	Becoming an Ethics Consultant	Tel: (808) 547-6050 Web: www.bioethicshawaii.org
3/12-3/16	HEM, OMM	Kirksville College of Osteopathic Medicine	Hilton Hawaiian Village, Honolulu	Primary Care Update	Tel: (660) 626-2232 Web: www.kcom.edu/
3/18-3/23	END	Mayo Clinic College of Continuing Medical Education	Hapuna Beach Prince Hotel, Kohala Coast	An Intensive Review of Endocrinology for the Clinician	Tel: (480) 301-4580 Web: www.mayo.edu/cme/
3/26-3/27	R	Stanford University School of Medicine	Hyatt Regency, Kaua'i	12th Annual Diagnostic Imaging Update in Hawai'i	Tel: (888) 556-2230 Web: http://med.stanford.edu
3/28-3/31	EM	Stanford University School of Medicine	Hyatt Regency, Kaanapali Beach, Maui	13th Annual Stanford Symposium on Emergency Medicine	Web: http://emedcme.stanford.edu/
3/29	NEP	Kaiser Permanente	Hawai'i Prince Hotel	Nephrology for the Non-Nephrologist	Tel: (808) 432-7931
April 2007					
4/3-4/5	P	State of Hawai'i Adult Mental Health Division	Hawai'i Convention Center, Honolulu	Work Works! Supported Employment: The 4th Annual Best Practices Conference	Tel: (808) 586-4686
4/08-4/13	PCP	University of California, San Francisco	Wailea Beach Marriott Resort & Spa, Wailea, Maui	Primary Care Medicine: Update 2007	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
4/10-4/12	Multi	Department of Orthopaedic Surgery, Kaiser Permanente	Grand Wailea Resort & Spa, Maui	15th Annual Update in Orthopaedic Surgery, Hawai'i 2007	Tel: (808) 432-2243
4/12-4/13	Multi	Kaiser Permanente	Hilton Waikiki Prince Kuhio Hotel, Honolulu	Palliative Care Conference	Tel: (808) 432-7931
4/15-4/20	DR	University of California, San Francisco	The Fairmont Orchid, Kamuela, Hawai'i	Diagnostic Imaging on Kona	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
May 2007					
5/18-5/19	Multi	Department of Native Hawaiian Health, University of Hawai'i	Hawai'i Prince Hotel	He Huliau – A Turning Point, Eliminating Health Disparities in Native Hawaiians & Pacific Peoples	Tel: (808) 587-8570
5/21-5/23	CD	Stanford Hospital & Clinics	Maui, HI	2nd Annual Complex Cardiovascular Patient Management	Tel: (650) 724-7166 Web: www.cme.stanfordhospital.com
June 2007					
6/11-6/15	ON, HO	University of Nebraska Medical Center	Grand Wailea Resort & Spa	2007 Pan Pacific Lymphoma Conference	Tel: (877) 832-6924 Email: conted@unmc.edu
6/16-6/21	OBG	University of California - Davis	Hapuna Beach Prince Hotel, Kohala Coast	UC Davis Women's Health Conference	Tel: (916) 734-5390
6/23-6/29	PD	University Children's Medical Group	Hyatt Regency Maui Resort, Maui	Pediatrics in the Islands… Clinical Pearls 2007	Tel: (800) 354-3263 Web: www.ucmg.org/cme.html

July 2007					
7/20-7/21	EM	The Queen's Medical Center	Hilton Hawaiian Village, Honolulu	Hawaiian Islands Trauma Symposium 2007	Tel: (808) 547-7009 Web: www.quuens.org/cme/
7/29-8/03	R	University of California, San Francisco	Fairmont Orchid Hawai'i, Kamuela	Breast Imaging	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
7/30-8/3	ORS	Department of Orthopaeadic Surgery, Kaiser Permanente Hawai'i	Grand Wailea Resort & Spa, Maui	15th Annual Update in Orthopaedic Surgery, Hawai'i 2007	Tel: (877) 843-8500 Web: www.cmxtravel.com
August 2007					
8/4	Multi	Hawai'i Chapter of the American College of Surgeons	JW Marriot Ihilani	2007 Summer Meeting	Tel: (808) 586-7446
8/5-8/11	IM, FM	Keck School of Medicine of USC	Ritz-Carlton Kapalua, Maui	50th Annual Refresher Course in Medicine	Tel: (800) 872-1119
8/9-8/10	Multi	Kaiser Permanente	Ihilani Resort & Spa, Honolulu	6th Annual Pai Symposium	Tel: (808) 432-7931
September 2007					
9/24-9/29	END	Mayo Clinic College of Continuing Medical Education	Hyatt Regency, Maui	20th Annual Techniques in Advanced Gynecologic, Endoscopic & Laparoscopic Surgery	Tel: (480) 301-4580 Web: www.mayo.edu/cme/
October 2007					
10/10-10/13	OMF	American Association of Oral and Maxillofacial Surgeons (AAOMS)	Hawaii Convention Center, Honolulu	89th Annual Meeting & Scientific Sessions	Tel: (847) 678-6200 Web: www.aaoms.org
10/16-10/20		American Society for Bone and Mineral Research	Hawai'i Convention Center, Honolulu	29th Annual Meeting	Tel: (202) 367-1161 Web: www.asbmr.org
10/18-10/20	GE	Stanford Hospital & Clinics	Mauna Lani Bay Resort, Kohala Coast	GI Cancers	Tel: (650) 724-7166 Web: www.cme.stanfordhospital.com
10/20-10/24	ORS	Orthopaedic Research Society	Hawai'i Convention Center, Honolulu	6th Combined Meeting of the Orthopaedic Research Societies	Tel: (847) 698-1625 Web: www.ors.org
10/22-10/27	GYN	Mayo Clinic College of Continuing Medical Education	Hyatt Regency, Maui	20th Annual Techniques in Advanced Gynecologic, Endoscopic & Laparoscopic Surgery	Tel: (480) 301-4580 Web: www.mayo.edu/cme/
November 2007					
11/10-11/13	Multi	American Medical Association	Hawai'I Convention Center, Honolulu	AMA Interim Meeting	Web: http://www.ama-assn.org/

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THE WEATHERVANE

RUSSELL T. STODD MD, CONTRIBUTING EDITOR

Russell T. Stodd MD

❖ **SHE SLEPT WITH AN OPHTHALMOLOGIST WHO KEPT ASKING, "IS IT BETTER LIKE THIS, OR LIKE THIS?"**

The eye surgeon went home after a busy day in the operating room where all the surgeries were smooth and uneventful. The following day the post-op patients were all suffering with corneal edema, diffuse anterior inflammation, and perhaps even fibrin or hypopyon in the anterior chamber. The condition is called toxic anterior segment syndrome (TASS), and the cause can be any of a number of operative problems, most commonly one of the solutions used to irrigate during the surgery. Over 100 cases were reported in the first half of 2006 alone. It can be wrong pH in the balanced salt solution, or epinephrine with preservative used to keep the pupil dilated rather than preservative-free, or gas residue when hand instruments are sterilized with ethylene oxide, or an anti-biotic with wrong concentration injected beneath the conjunctiva at the end of surgery leaking into the eye. It can be catastrophic for both patient and doctor, and determining the exact cause can be complicated and difficult. Stuff happens!

❖ **NEVER LET THE DOCTOR TAKE YOUR TEMPERATURE WITH HIS FINGER.**

For many years we have had "doc in the box" medical care with clinics usually set up in tourist areas which provide walk-in physician care. They are often frustrating competition for local practitioners, but usually do a fair job for emergency problems. Now we have RBCs, retail based clinics at Wal-Mart and Target stores, caring for patients at the mall or shopping center. The nice part for patients is the ease of seeing a medical person, and the nice part for the clinics is that it is all cash, no insurance forms, no detailed coding baloney, and regular hours. Recently, the American Academy of Pediatrics and the American Medical Association spoke out against RBCs, claiming that medical care is fragmented with poor follow-up and loss of continuity. This is true, of course, but the problem really generates from crowded doctors' schedules, prolonged waiting in reception areas and delays in getting appointments. So, get used to it, people. It is free enterprise at work at the mall.

❖ **"IF WE WANT OUR COMPANY TO SURVIVE AND PROSPER OVER THE LONG TERM, WE MUST GET OUR SHARE OF THE YOUTH MARKET." R. J. REYNOLDS INC. 1974**

The tobacco people do not sleep. "Snus" is a smokeless tobacco product popular in Scandinavia for decades, but banned in most of Europe as an oral carcinogen. Now R.J. Reynolds is test marketing "Camel Snus" in Portland, Oregon, and Austin, Texas, two communities viewed as "hipster havens." The product is put up in small neat pouches of 20 per tin. They smell of mint tea, taste like gum and come in three flavors, regular, spice, and frost, with packets that fit inside the mouth. Supposedly, they are spit-free as well as smoke-free. Of course, they are not designed to appeal to youth. Right!! The s*nuscamel.com* website says you can use it at a concert, in a jet plane, even at a crowded up-scale restaurant. How about a teenager in a classroom?

❖ **MAN IS THE ONLY MACHINE THAT NEEDS TO BE LUBRICATED WITH ALCOHOL.**

The national average for alcohol-related traffic deaths is 39%. Ugly! What is even more ugly is that right here in our Aloha state the figure is actually 51%, twelve full percentage points above the national average, and that places us right at the top (really the bottom) of all 50 states. Only Washington D.C. is ahead of Hawai'i at 54%. Look at the celebrities arrested for DUI, starting with Mel Gibson, comedic actors Rip Torn and Tracey Morgan, and Michelle Rodriguez, who was jailed here for five hours (that's all) of a 60-day sentence for repeat DUI, to mention just a few. The sport star arrests would fill up a phone book, including Sacramento Kings head coach Eric Musselman**.** These are supposed to be responsible citizens. And as a responsible physician, what action do you take (if any) when you detect alcohol on your patient's breath? Obviously, if the DUI highway slaughter is to be stemmed, the offenders must be jailed, and their drivers' licenses and auto licenses impounded. A modest fine, a suspended jail sentence, and probation are fruitless.

❖ **IT'S NOT ENOUGH TO HAVE NEED. FOR MEDICAL CARE IN HAWAI'I, YOU HAVE TO EARN A CERTIFICATE!**

The Hawai'i comprehensive health planning law which provides for "certificate of need" (CON) for certain medical expenditures is under severe attack by many citizens on the island of Maui. Ronald Kwon MD, Hawai'i born, Harvard educated, and a long-time infectious disease specialist on the island, in partnership with Triad Hospitals (ranked number four by Fortune magazine among America's most admired health care companies) applied for a CON to build a second hospital in south Maui. The plan has the vigorous support of the Mayor of Maui County, Governor Linda Lingle, many Maui physicians and a large and varied group of people. After a complicated and prolonged application, followed by a stair-step collection of hearings and one re-hearing, the application was denied. Wow!! The passion and animosity toward the director of SHPDA (State Health Planning and Development Agency), people on the panels, and Hawai'i Health Systems Corporation, which is perceived as the primary obstructionist, was palpably frightening. What next? Apparently further steps are in the works, but the underlying cause of the mess is the absurd health planning law which does not exist in many states. In Ohio and Illinois similar statutes have resulted in bribery with criminal prosecutions. For valid reasons, both the AMA and HMA have policy opposing state health planning laws, but don't expect it to disappear. It is far easier to eradicate Mt. Rushmore than a government bureau. SHPDA lives on!

❖ **YOUTH IS LIKE SPRING; TRANSIENT, EXAGGERATED, AND WITH THE ATTENTION SPAN OF LINT.**

We all knew it was coming, and now the hearing loss in young adults has arrived. At the University of California Irvine Medical Center, the effects of the MP3 player which comes with stock "ear buds" has apparently caused damaged hearing in several students. Normally this type of loss would not be seen until 50 or 60 years of age. The sound is digital and kids can crank up the volume without the distortion of previous technologies. Unlike the previous portable headset music players, the MP3 has buds which close off the ear canal and do not allow sound to escape.

❖ **HEY! HAS ANYBODY SEEN MY BAYONET?**

In the realm of unbelievable medical errors, a Seattle man had abdominal surgery for a tumor. For two months after surgery he complained of pain, but apparently no further studies were performed. When he failed to clear an airport metal detector, x-ray revealed a thirteen (!) inch blade in his abdomen. He won $105,000 in a court settlement; a fair payday for intermittent pain. His attorney said, "It was like missing a truck parked in your front yard."

❖ **MONEY CAN BE LOST IN MORE WAYS THAN WON.**

According to the Super Bowl Predictor of investments, 2007 is expected to see a rise in stocks. Yes, this completely unscientific indicator has been accurate in 80% (32 of 40) bowls. The factor is whenever an "original" National Football League team wins the big game, e.g. San Francisco, Chicago, Green Bay, the Dow Jones Industrial Average goes up for that year. The market falls when the team is a later addition to the league, e.g New England, Denver. Since both teams, Indianapolis (nee Baltimore) Colts and Chicago Bears are original franchises, your blue chip investments are given a four out of five prediction to rise. Sleep well on your blue chips.

ADDENDA

❖*Fish 'n Flush* is a toilet that doubles as an aquarium. (I did not make this up!)

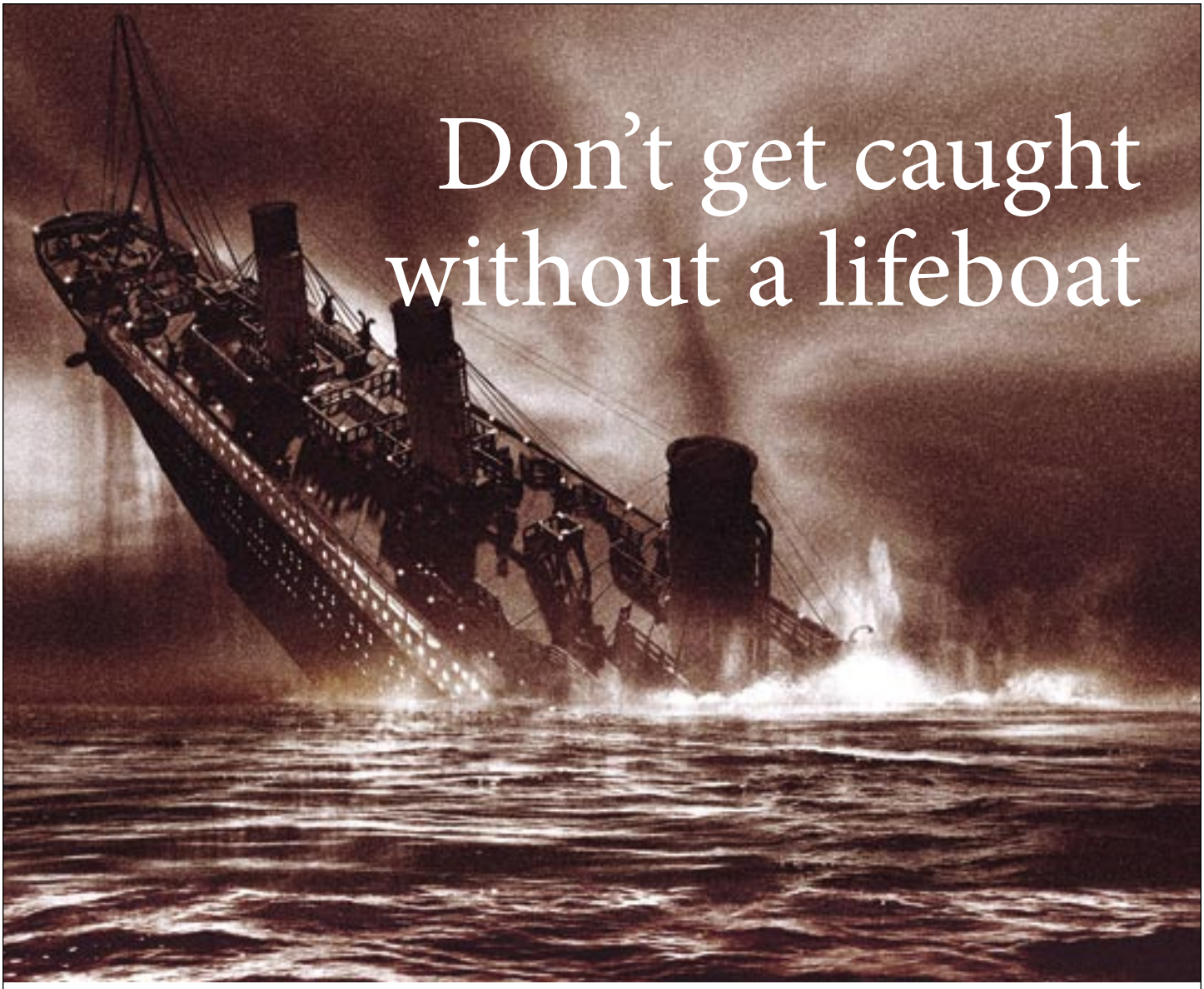
❖Headline in the Salt Lake Tribune, "Utah risks loosing its best teachers." I think this warning is a bit tardy.

❖Wine is mentioned in every book of the Bible except Jonah.

❖What's medically good for you depends on who sponsors the study.

ALOHA AND KEEP THE FAITH — rts■

Contents of this column do not necessarily reflect the opinion or position of the Hawai'i Ophthalmological Society and the Hawai'i Medical Association. Editorial comment is strictly that of the writer.



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