Analysis of causes that led to Christine Maggiore's acute renal and cardiac failure, pulmonary edema, and death

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Abstract

Christine Maggiore was diagnosed with pneumonia on December 18, 2008 and was treated with antibiotics (Gentamicin, Rocephin, Azithromycin), Acyclovir, Fluconazole and corticosteroids. She also received Meyer's cocktail, vitamin C, and calcium IV. She died on December 27,2008. She was 52 years of age.

Christine suffered fatal renal failure caused by antibiotics, antiviral, and calcium received during the 9 days prior to her death. The microscopic examination of the H & E stained sections of her kidneys revealed the presence of changes consistent with acute tubular necrosis. There were also changes consistent with mild nephrosclerosis.

Christine's acute renal failure led to development of acute left ventricular heart failure, pulmonary congestion, and pulmonary edema. Christine's pericardial sac and left chest cavity contained 100 mL and 200 mL of clear light brown serious fluid, respectively. Christine's right and left lungs weighted 1319 and 1307 g, respectively. Her total lung weight was 2626 g, which is 750% of the average normal lung weight.

The autopsy, pathology, and the clinical data and observation described in this report show clearly that Christine did not suffer from any AIDS indicator illness during the 2 years prior to her death or at the time of her death. The gross and microscopic examination of Christine lymphoid organs and bone marrow appeared normal. The growth of P. jiroveci observed in Christine's lungs and other tissues resulted from her treatment with corticosteroids during the 9 days prior to her death.

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Summary of the case and findings

Christine Maggiore was diagnosed with pneumonia on December 18, 2008 and was treated with antibiotics (Gentamicin, Rocephin, Azithromycin), Acyclovir, Fluconazole and corticosteroids. She also received Meyer's cocktail, vitamin C, and calcium IV. She died on December 27, 2008. She was 52 years of age.

Dr. David M. Posey performed the autopsy in Christine's case and his gross autopsy examination was completed on January 12, 2009. He stated that Christine was a well-developed and well-nourished Caucasian woman who appeared younger than her age of 52 years. She measured 66 inches in length and weighed 145 pounds.

Examination of Christine's chest and abdominal cavities revealed that her organs were normally placed with no adhesions in these cavities noted. Her pericardial sac and left chest cavity contained 100 mL and 200 mL of clear light brown serous fluid, respectively.

Dr. Posey's gross examination of Christine's lungs revealed severe pulmonary edema and congestion. Christine's right and left lungs weighted 1319 and 1307 g, respectively. His microscopic examinations of H & E stained sections of her lungs demonstrated severe congestion and edema. There was marked alveolar distention by frothy eosinophilic proteinaceous exudates. Diffuse alveolar damage was noted in both lungs. There was also proliferation of type 2 pneumocytes with modest infiltrates of acute and chronic inflammatory cells.

Posey's microscopic examination of Christine's organs revealed the following abnormalities in her kidneys, heart, liver, and thyroid gland: a) The presence of changes consistent with acute tubular necrosis in both kidneys. There were also changes

consistent with mild nephrosclerosis; b) mild interstitial edema in the heart; c) benign focal nodular hyperplasia in the liver; and d) microscopic benign follicular adenoma in the thyroid gland.

In addition, growth of Pneumocystis jiroveci (carinii) was observed on the H & E stained sections of lungs, liver, pancreas, spleen, kidneys, and bone marrow and confirmed on the Gomori methenamine silver (GMS) preparation. The gross and microscopic examinations of Christine's brain, thymus, spleen, lymph node, bone marrow, brain, and other organs were unremarkable.

Christine's husband and his attorney requested that I evaluate the medical evidence in Christine's case and give my opinion concerning the likely causes that led to her illness and sudden death. I am a toxicologist and pathologist with over 20 years experience in these fields. I have evaluated many cases of children and adults who died suddenly from unexplained causes and cases of children and adults who suffered from acute and/or chronic illnesses. I was able to explain the causes of illnesses and death in these cases using differential diagnosis.

I have also served as an expert witness in many medical-legal cases involving children and adults. I have published over 45 articles in medical and scientific journals.
I evaluated Christine's medical records, autopsy report, and the pertinent articles cited in this report using differential diagnosis. My investigation in this case reveals the following:

1) Christine suffered fatal renal failure caused by the medications received during the 9 days prior to her death as indicated by the clinical and medical studies described in Section IV of this report. Briefly;

a) Christine was treated with high therapeutic doses of gentamicin (600 mg/day) for 9 days prior to her death and gentamicin is documented in the medical literature to cause tubular necrosis in individuals treated with similar doses (Section IV-A).

For example, Buchholtz et al. conducted a prospective observational cohort study to quantify the nephrotoxic effect of gentamicin. A total of 287 (77%) of the patients received gentamicin treatment (median duration, 14 days); dosage was adjusted according to daily serum creatinine and trough serum gentamicin levels. Kidney function was determined by estimated endogenous creatinine clearance (EECC). In the gentamicin group, the mean EECC change was an 8.6% decrease, but in the no-gentamicin group, the mean change was an increase of 2.3% (P = .05). The decrease in EECC was significantly correlated with the duration of gentamicin treatment: a 0.5% EECC decrease per day of gentamicin treatment (P = .002)

b) Christine was treated with Rocephin (ceftriaxone) at 1 g/day twice daily and calcium solution IV for several days prior to her death. The treatment of ceftriaxone with calcium is contraindicated. In June 2007, the US FDA advised that in patients of all ages, calcium-containing solutions should not be administered simultaneously or within 48 hours of the last ceftriaxone dose. The FDA received reports on neonatal and infant deaths associated with ceftriaxone-calcium precipitation in the lungs and kidneys (Section IV-A).

c) Christine was treated with high therapeutic doses of acyclovir (800 mg twice daily) for 5 days prior to her death and acyclovir has known to cause kidney damage in individuals treated with similar doses (Section IV-B).

For example, Pacheco et al. evaluated the incidence and outcome of acute renal failure (ARF) in 41 individuals (over 13 years of age) received IV acyclovir for 5 or more days.

When serum creatinine levels, previously in the normal range, increased above 2 mg/dL, the case was considered an ARF. ARF developed in 8 out of 41 individuals (19.5%). In the ARF cases, after beginning of treatment, the average time for increase of the serum creatinine levels was 4.2 days. Creatinine levels reached their peak in a mean time of 7.1 days (ranging from 3 to 14 days). Recovery of the renal function, evaluated by decrease of the creatinine level, varied from 1 to 7 days (mean of 3.6 days).

d) Christine's autopsy weight was 145 pounds, which is 20.8% higher than her normal weight of 120 pounds measured during the 2 years prior to her death. It indicates that she suffered from fluid retention due oliguria/anuria caused by renal failure. No blood and urine tests were performed during the 9 days prior to Christine's death to monitor for drug toxicity (Section IV).

e) Blood and urine tests performed on December 15, 2006 and November 9, 2007 showed that Christine's kidneys were working fine. She was not suffering from electrolytes imbalance, urinary tract infection, or kidney problems (Section I-D).

2) Christine's acute renal failure led to development of acute left ventricular heart failure. Acute tubular necrosis usually produces a variety of clinical consequences affecting the entire body, including hyperkalemia, acidosis, hypocalcemia, and anemia, as well as various cardiovascular, neurologic, gastrointestinal problems, and death (Section V-A).

Christine's pericardial sac and left chest cavity contained 100 mL and 200 mL of clear light brown serious fluid, respectively. Normally, the pericardial sac contains up to 30 ml of clear fluid. In left-sided heart failure, transudate accumulates within the pleural spaces frequently, particularly, on the left side, producing a gross pleural effusion. A chest X-ray performed on December 18, 2008, prior to Christine's treatment with medications and

calcium did not show that she had abnormal fluid in her pericardial sac and left chest cavity.

Posey examined Christine's heart grossly and appeared normal. Her heart weighted 329 g. In the female, the average weight of the heart is 250 to 300 g. His microscopic examination of the H & E stained sections of Christine's heart demonstrated mild interstitial edema, but otherwise was unremarkable.

There was no evidence of recent or remote myocardial infarct or damage observed in Christine's heart and the sinoaterial node was unremarkable. A blood test performed at 2 years prior to Christine's death showed that she had a very low risk for cardiovascular disease (Section I-C).

Schär et al. reported the case of a 50-year-old female in whom the connection between hypocalcemia and heart failure was not made until a second hospital admission for left ventricular failure. Under appropriate calcium supplementation the symptoms were relieved within 2 days and the woman remained well thereafter (Section V-A).

3) Christine suffered from severe pulmonary edema due to her left ventricular heart failure. Her total lung weight was 2626 g, which is 750% of the average normal lung weight. The average normal weight of human lung is 300 to 400 g. A chest X-ray performed on December 18, 2008, prior to Christine's treatment with medications and calcium did not show that she had pulmonary edema and abnormal fluid in her pericardial sac and left chest cavity (Section V-B).

Posey's microscopic examination of the H & E stained tissue sections of Christine's lungs demonstrate severe congestion and edema. All sections from both lungs showed marked alveolar distention by frothy eosinophilic proteinaceous exudates. Pulmonary edema has been reported in individuals are suffering from heart failure.

In heart failure, there is an increase in pulmonary venous and capillary pressure and therefore in the forces moving fluid into the interstitium of the lung. Simultaneously the interendothelia junction stretches are widened, allowing the increased movement of both fluid and macromolecules into the interstitium.

When critical elevations in interstitial pressure are reached or increased pressure is prolonged so that the tight junctions between alveolar lining epithelial cells break and alveolar edema results. Posey's microscopic examination of section of Christine's lung stained with PSA showed evidence of early onset of diffuse alveolar damage characterized by widening and edema of the alveolar septae.

Kazmi and Wall evaluated a case of a 71-year-old man presented with acute pulmonary edema related to new onset of severe left ventricular dysfunction (ejection fraction, 30%). His symptoms did not improve with emergency therapy with diuretics and dobutamine. He was noted to be severely hypocalcemic (5.5 mg/dL) and subsequently showed dramatic improvement in symptoms and ejection fraction (58%) with correction of hypocalcemia with intravenous calcium and calcitriol replacement.

4) Medications given to Christine on December 18-26, 2008 are the likely causes for the benign lesions observed in her thyroid gland and liver as indicated by the clinical studies and observation described in Section VI of this report.

5) The growth of P. jiroveci in Christine's lungs and other tissues resulted from her treatment with corticosteroids during the 9 days prior to hear death as indicated by the clinical observations and studies described in Section VII of this report. Briefly;
a) Dr. Posey examined Christine's lymphoid organs and bone marrow grossly and microscopically, which appeared normal.

b) The presence of P. jiroveci in Christine's lungs and other organs were not associated with any pathological lesion. P. jiroveci has known to cause interstitial pneumonia in individuals suffering from severe immunosuppression. Christine did not have interstitial pneumonia and the edema observed in her lungs resulted from her heart and renal failure induced by medications.

c) P. jiroveci is found in the respiratory system of healthy individuals. Treatment with therapeutic doses of corticosteroids for a significant time promotes its growth.

d) Blood analyses performed during the 2 years prior to Christine's death revealed that her hematology values, white blood cells, and differential counts were within the normal range.

6) The autopsy, pathology, and the clinical data and observation described in this report show clearly that Christine did not suffer from any AIDS indicator illness during the 2 years prior to her death or at the time of her death. It has been reported that Christine's serum was tested positive for HIV with subsequent testing indeterminate in the 1990s. The clinical findings in Christine's case clearly challenge the clinical and scientific validity of the HIV test, if it is intended as a certain marker of gradual immune demise, which she did not manifest.

Section I. Christine's health condition during the 2 years prior to her respiratory illness of December 2008

The review of Christine's medical records for the period between December 1, 2006 and October 17, 2008 shows that she was in a good health except for complaints of having skin rash, hot flashes, and symptoms of menopause. She used acupuncture and took vitamin C, alpha lipoic acid, DHEA, calcium, magnesium drink, and herbal supplements to relieve her symptoms. She also applied Tamanu oil (Calophyllum inophyllum) on her skin to treat the skin rash.

Christine used to exercise regularly and walked 3-4 miles per day and 3-4 times per week. Christine's height was 66 inches and her weight on December 1, 2006 and October 17, 2008 was 118 and120 pounds, respectively [1].

In addition, blood and urine tests performed on December 15, 2006 and November 9, 2007 showed that Christine's immune system, bone marrow, liver, kidney, and endocrine glands were working fine and she had low risk for cardiac disease (Tables 1-9). Below are the results of these tests and their significances.

I-A. Normal bone marrow and immune functions tests

Blood analyses performed on December 15, 2006 and November 9, 2007 revealed that Christine did not suffer from anemia, thrombocytopenia, or iron deficiency (Table 1). In addition, her white blood cells and differential counts were within the normal range. She did not suffer from infections, leukocytopenia, or lymphocytopenia (Table 2). These data indicate that Christine had normal bone marrow and immune functions.

Table 1. Christine's hematology values measured on December 15, 2006 and November 9, 2007

Measurements	12/15/06	11/09/07	Ref. Range
Red blood cells x $10^6/\mu L$	4.23	4.16	3.80-5.10
Hemoglobin (g/dL)	13.0	13.1	11.7-15.5
Hematocrit %	39.1	37.9	35.0-45.0
MCV (FL)	92.4	91.1	80-100
MCH pg	3.07	31.5	27.0-33.0
MCHC (g/dL)	33.2	34.6	32.0-36.0
RDW %	12.9	12.1	11.0-15.0
Total iron (µg/dL)	93	78	35-175
Ferritin (ng/mL)	0.43	-*	10-232
Platelet x $10^3/\mu L$	272	266	140-400
White blood cells x $10^3/\mu L$	4.7	3.7	3.8-10.8

*-: Not measured

Table 2. Christine's white blood cell differential counts measured on December 15, 2006 and November 9, 2007

Measurements	12/15/06	11/09/07	Ref. Range
White blood cells x $10^3/\mu L$	4.7	3.7	3.8-10.8
Neutrophils %	55.5	79.6	50-70
Lymphocytes %	22.6	21.4	15-45
Monocytes %	10.0	10.9	0-10
Eosinophils %	11.4	8.6	0-6
Basophils %	0.5	1.2	0-2

I-B. Normal endocrine functions tests

Blood tests performed on December 15, 2006 showed that a) Christine's TSH, T3, and T4 levels were within the normal range and she did not have thyroid problems (Table 3); b) her female hormonal panel was within the normal range (Table 4); and c) she did not

suffer from diabetes or autoimmune illness (Table 5). In addition, Christine's blood tests of November 9, 2007 revealed that her thyroid was working fine (Table 3) and she had a normal glucose level of 81 mg/dL.

Table 3. Christine's thyroid function tests performed on December 15, 2006 and November 9, 2007

Measurements	12/15/06	11/09/07	Ref. Range
T4, free	0.9	1.0	0.8-1.8 ng/dL
T3, free	272	267	230-420 pg/dL
TSH	1.54	2.40	0.4-5.50 mIU/L

Table 4. Christine's hormonal levels measured in blood on December 15, 2006

Measurements	Values	Ref. Range
FSH	68.5	23.0-116.3 mIU/mL*
Estrogen (Total)	111	130 pg/mL or less*
Progesterone	0.7	<0.7 ng/mL*
Pregnenolone	36	10-230 ng/dL
DHEA Sulfate	65	15-170 µg/dL
Testosterone (Total)	24	20-76 ng/dL (adult female)

*Postmenopausal

Table 5. Christine's blood levels of glucose, hemoglobin Alc, and antibodies measured on December 15, 2006

Measurements	Values	Ref. Range
Plasma glucose	108	< 120 mg/dL
Hemoglobin Alc	5.2	Non-Diabetic: <6.0%
Antinuclear antibody (ANA)	Negative	Negative
Rheumatoid factor	5	<14 IU/mL

I-C. Low risk for heart disease

Blood tests performed on December 15, 2006 and November 26, 2007 showed that Christine had very low risk for cardiac disease (Table 6). In addition, her blood test of November 9, 2007 revealed that she had a creatine kinase enzyme level of 61 U/L (normal range: < or =165 U/L), which indicates that she did not have heart or skeletal muscle damage.

Table 6. Christine's indicators for low risk of having cardiovascular disease

Measurements	12/15/06	11/26/07	Ref. Range
Triglycerides	78	71	<150 mg/dL
Total Cholesterol	187	197	<200 mg/dL
HDL Cholesterol	64	59	> or =40 mg/dL
LDL Cholesterol	107	126	<130 mg/dL
Cardio C-reactive protein	0.7		<1.0 mg/L (LRCD)* 1.0-3.0 mg/L (ARCD)**

* LRCD: Low risk for cardiovascular disease
** Average risk for cardiovascular disease

I-D. Normal liver, kidney, and parathyroid glands functions tests

Blood and urine tests performed on December 15, 2006 and November 9, 2007 showed that Christine's liver and kidneys were working fine (Tables 7-9). In addition, Christine's serum levels of phosphorous, calcium, vitamin D, and alkaline phosphatase enzyme were within normal range which indicate that she did not have parathyroid glands or bone problems (Tables 7, 8). Furthermore, her urine analyses indicate that she did not suffer from urinary tract infections (Table 9).

Table 7. Christine's serum enzymes, protein, BUN, uric acid, and bilirubin Levels measured on December 15, 2006 and November 9, 2007

Measurements	12/15/06	11/09/07	Reference Range
Albumin	4.4	4.5	3.5-4.9 g/dL
Globulin	3.4	3.2	2.2-4.2 g/dL
T. Protein	7.8	7.7	6.0-8.3 g/dL
Urea Nitrogen (BUN)	11	15	7-25 mg/dL
Uric acid	5.4	5.0	1.7-7.5 mg/dL
Total bilirubin	0.6	0.5	0.2-1.3 mg/dL
Lactic dehydrogenase	155	189	100-250 U/L
Alanine aminotransferase	30	28	3-40 U/L
Gamma glutamyl transpeptidase	25	-*	3-60 U/L
Alkaline phosphatase	77	67	20-125 U/L
Aspartate aminotransferase	25	26	3-35 U/L

-*: Not measured

Table 8. Christine's serum electrolytes, creatinine, and vitamin D levels measured on December 15, 2006 and November 9, 2007

Measurements	12/15/06	11/09/07	Reference Range
Sodium	140	137	135-146 mmol/L
Potassium	5.2	4.3	3.5-5.3 mmol/L
Chloride	104	102	98-110 mmol/L
Calcium	10.0	9.8	8.5-10.4 mg/dL
Magnesium	1.9	1.9	1.5-2.5 mg/dL
Phosphorous	3.9	3.6	2.5-4.5 mg/dL
Creatinine	0.9	0.8	0.5-1.2 mg/dL
Vitamin D, 25-hydroxy	60	-*	20-100 ng/mL

*-: Not measured.

Table 9. Christine urine analyses performed on December 15, 2006 and November 9, 2007

Measurements	12/15/06	11/09/07	Reference Range
Color	Yellow	Yellow	Yellow
Appearance	Clear	Clear	Clear
Specific Gravity	1.011	1.007	1.001-1.035 (g/mL)
pH	7.5	6.0	5.0-8.0
Glucose	Negative	Negative	Neg.
Bilirubin	Neg.	Neg.	Neg.
Ketones	Neg.	Neg.	Neg.
Occult Blood	Neg.	Neg.	Neg.
Protein	Neg.	Neg.	Neg.
Nitrite	Neg.	Neg.	Neg.
Leukocyte Esterase	Neg.	Neg.	Neg.
WBC	None seen	None seen	< or = 5/HPF
RBC	None seen	None seen	< or =3/HPF
Sequamous Epithelial cells	None seen	None seen	< or =5/HPF
Bacteria	None seen	None seen	None seen/HPF
Hyaline cast	None seen	None seen	None seen/HPF

Section II. Christine's respiratory illness of December 2008 and treatments received during the 9 days prior to her death

Christine was coughing, feeling tired, and had low-grade fever on December 2, 2008. She consulted with her holistic health provider. She was treated with herbal medicine and other supplements during the period of December 2-15, 2008. However, her symptoms did not improve [1].

Christine consulted with her physician on December 18, 2008. A chest X-ray performed on December 18th and revealed that Christine had evidence of pneumonia. There were patchy interstitial infiltrates in both mid and lower lung fields.

Christine was treated with corticosteroids, three antibiotics and antiviral and antifungal agents for nine days. In addition, she received Meyer's cocktail, vitamin C, and calcium IV (Table 10). No blood and urine tests were performed to monitor for liver, kidney, heart, and lung toxicity of these medications [2, 3].

Christine died at 1630 on December 27, 2008 and Dr. David M. Posey performed the autopsy. Autopsy was performed in La Crescenta California. The gross autopsy examination was completed at 1530 on January 12, 2009 [4]. Dr. Posey's autopsy and pathology findings are described in Section III of this report.

Table 10. Medications and supplements given to Christine during the 9 days prior to her death

Date	Treatments given
12/18/08	**Antibiotics:** Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice daily. **Corticosteroids:** Solu medrol (methylprednisolone) 125 mg IV. **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/19/08	**Antibiotics:** Gentamicin 600 mg twice daily; Rocephin (Ceftriaxone) 1 gram IV twice daily. **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/20/08	**Antibiotics:** Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice daily. **Corticosteroids:** Pulvicort 180 µg/dose **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/21/08	**Antibiotics:** Azithromycin (250 mg twice daily); Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice a day. **Corticosteroids:** methylprednisolone 8 mg; Pulvicort 180 µg/dose **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/22/08	**Antibiotics:** Azithromycin (250 mg twice daily); Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice a day. **Antiviral:** Acyclovir 800 mg twice daily **Corticosteroids:** methylprednisolone 8 mg; Pulvicort 180 µg/dose **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/23/08	**Antibiotics:** Azithromycin (250 mg twice daily); Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice a day. **Antiviral:** Acyclovir 800 mg twice daily **Corticosteroids:** methylprednisolone 8 mg; Pulvicort 180 µg/dose **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/24/08	**Antibiotics:** Azithromycin (250 mg twice daily); Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice a day. **Antiviral:** Acyclovir 800 mg twice daily **Corticosteroids:** methylprednisolone 8 mg; Pulvicort 180 µg/dose **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/25/08	**Antibiotics:** Azithromycin (250 mg twice daily); Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice a day. **Antiviral:** Acyclovir 800 mg twice daily **Corticosteroids:** methylprednisolone 8 mg; Pulvicort 180 µg/dose **Antifungal:** Fluconazole 200 mg **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.
12/26/08	**Antibiotics:** Azithromycin (250 mg twice daily); Gentamicin 600 mg; Rocephin (ceftriaxone) 1 gram IV twice a day. **Antiviral:** Acyclovir 800 mg twice daily **Corticosteroids:** methylprednisolone 8 mg; Pulvicort 180 µg/dose **Antifungal:** Fluconazole 200 mg **Supplements:** Meyer's Cocktail, vitamin C 10 g, calcium 15 mL, IV.

Section III. Autopsy and pathology findings in the case of Christine Maggiore

Christine died on December 27, 2008 and Dr. David Posey performed the autopsy. He stated that Christine was well-developed and well-nourished Caucasian woman who appeared younger than the listed age of 52 years. She measured 66 inches in length and weighed 145 pounds [4].

Christine's skin was unremarkable, except for a 2.5 and 3.5 inches area of excoriation on her left upper lateral buttock. No evidence of external injury was noted. The examination of her skeletal muscles and bones were unremarkable.

Examination of Christine's chest and abdominal cavities revealed that her organs were normally disposed with no adhesions in these cavities were noted. Her pericardial sac contained 100 mL of clear light brown serous fluid. In her left chest cavity, there were 200 mL of clear, serous, golden-brown fluid, but there was no abnormal fluid in the right chest cavity or in her abdominal cavity.

Dr. Posey's gross and microscopic examinations of Christine's organs revealed the abnormal changes described below in her kidneys, heart, lungs, trachea, liver, and thyroid glands. In addition, growth of Pneumocystis jiroveci (carinii) was observed on the H & E stained sections of lungs, liver, pancreas, spleen, kidneys, and bone marrow and confirmed on the Gomori methenamine silver (GMS) preparation. The gross and microscopic examinations of other organs were unremarkable (Table 11).

1) A simple 1.5 cm cyst filled with clear yellow fluid was found in the cortex of Christine's left kidney. The weight of Christine's right and left kidneys was 110 and 169 g, respectively.

The microscopic examination of the H & E stained sections of Christine's kidneys revealed the presence of changes consistent with acute tubular necrosis in both kidneys. There were also changes consistent with mild nephrosclerosis.

2) The gross examination of Christine's heart appeared normal and her heart weight was 329 g. The microscopic examination of the H & E stained sections of Christine's heart demonstrated mild interstitial edema, but otherwise her heart was unremarkable.

3) Christine's right and left lungs weighted 1319 and 1307 g, respectively. On sectioning, the firm, dark red beefy parenchyma demonstrated marked congestion and edema. The microscopic examination of H & E stained tissue sections of Christine's lungs demonstrate severe congestion and edema.

All sections from both lungs showed marked alveolar distention by frothy eosinophilic proteinaceous exudates. Diffuse alveolar damage was noted in both lungs. There was also proliferation of type 2 pneumocytes with modest infiltrates of acute and chronic inflammatory cells.

4) Microscopic examination of H & E section of Christine's trachea demonstrated autolytic changes with submucosal edema and mild vascular congestion. There was also minimal inflammatory infiltrates.

5) The examination of Christine's liver revealed the presence of benign focal nodular hyperplasia.

6) The examination of Christine's thyroid gland revealed the presence of microscopic benign follicular adenoma.

My review of Christine's medical records, autopsy report, and the pertinent medical literature indicate the following:

1) Christine suffered acute renal failure caused by the medications received during the 9 days prior to her death (Section IV).

2) Her acute kidney failure led to the development of left ventricular heart failure and severe pulmonary congestion and edema (Section V).

3) The likely causes of the benign focal nodular hyperplasia noted in Christine's liver and the microscopic benign follicular adenoma observed in her thyroid glands were also the medications received during the 9 days prior to her death and metabolic changes (Section VI).

4) The growth of Pneumocystis jiroveci (carinii) observed in Christine's lungs, liver, pancreas, spleen, kidneys, and bone marrow was caused by her treatment with corticosteroids received during the 9 days prior to her death as explained in Section VII.

Table 11. Christine's organs that showed no abnormalities

Organs	Gross Examinations	Microscopic examination (H & E stained section)
Brain	Unremarkable Weighted 1358 g	Unremarkable
Pituitary gland	Unremarkable	Unremarkable
Parathyroid glands	Unremarkable	Unremarkable
Thymus	Normal for age	-*
Ovaries	Unremarkable	-
Fallopian tubes	Unremarkable	-
Uterus	Unremarkable	Unremarkable
Spleen	Unremarkable dark red-purple Weighted 189 g	Mildly congested
Lymph nodes	Normal size and consistency	A section of lymph node was unremarkable.
Bone Marrow	Red and moist	Demonstrated normal trabeculae and appeared to have normal cellularity.
Adrenal glands	Unremarkable	Unremarkable
Gallbladder	Unremarkable	-
Pancreas	Unremarkable	Unremarkable
GI tract	Unremarkable	Sections of esophagus, stomach, duodenum, small bowel, and colon were unremarkable.
Urinary bladder	Unremarkable	-

-*: Not examined

Section IV. The likely causes of Christine's acute bilateral renal failure

Dr. Posey examined Christine's kidney grossly and microscopically. The weight of her right and left kidneys was 110 and 169 g, respectively. The weight of Christine's right kidney is below the average normal weight of 150 g [5].

The microscopic examination of the H & E stained sections of Christine's kidneys revealed the presence of changes consistent with acute tubular necrosis in both kidneys. There were also changes consistent with mild nephrosclerosis. These acute injuries led to bilateral renal failure and oliguria.

Christine had suffered from pneumonia and was treated with antibacterial, antiviral, and antifungal medications and calcium on December 18-26, 2008 (Table 10). She died on December 27, 2008. The clinical and medical studies described below indicate that Christine's renal failure was caused by the medications received during the 9 days prior to her death.

1) Christine was treated with high therapeutic doses of gentamicin (600 mg/day) for 9 days prior to her death and gentamicin has known to cause tubular necrosis in individuals treated with similar doses (Section IV-A).

2) Christine was treated with Rocephin (ceftriaxone) at 1 g/day twice daily and calcium solution IV for several days prior to her death. The treatment of ceftriaxone with calcium is contraindicated. In June 2007, the US FDA advised that in patients of all ages, calcium-containing solutions should not be administered simultaneously or within 48 hours of the last ceftriaxone dose. The FDA received reports on neonatal and infant deaths associated with ceftriaxone-calcium precipitation in the lungs and kidneys [6, 7].

3) Christine was treated with high therapeutic doses of acyclovir (800 mg twice daily) for 5 days prior to her death. Acyclovir has known to cause kidney damage in individuals treated with similar doses (Section IV-B).

4) Christine's autopsy weight was 145 pounds, which is 20.8% higher than her normal weight of 120 pounds measured during the 2 years prior to her death (Table 12). It indicates that she suffered from fluid retention due oliguria/anuria caused by renal failure. No blood and urine tests were performed during the 9 days prior to Christine's death to monitor for drug toxicity.

5) Blood and urine tests performed on December 15, 2006 and November 9, 2007 showed that Christine's kidneys were working fine. She was not suffering from electrolytes imbalance, urinary tract infection, or kidney problems (Section I-D).

Table 12. Christine's weight and height measured during 2 years prior to death and at autopsy

Date	Weight (Pounds)	Height (Inches)
12/01/06	118	66
11/26/07	119	66
12/18/07	120	66
10/19/08	120	66
12/27/08*	145	66

Christine's autopsy weight was 145 pounds.

IV-A. Nephrotoxicity of Gentamicin

Gentamicin (GM) is an aminoglycoside used to treat gram-negative and Gram-positive bacterial infections. However, its clinical use is limited by its nephrotoxicity [8-21].

GM-induced nephrotoxicity was recorded by increased serum creatinine and blood urea nitrogen [18].

Christine was treated with GM at 600 mg per day for 9 days prior to her death in addition to other medications (ceftriaxone with calcium, acyclovir, and fluconazole) that are known to cause kidney problems. However, Christine's blood levels of creatinine, urea nitrogen (BUN), and electrolytes were not measured to check for kidney problems.

Posey's microscopic examination of the H & E stained sections of Christine's kidneys revealed the presence of changes consistent with acute tubular necrosis in both kidneys. Christine's autopsy weight of 145 pounds is 20.8% higher than her normal weight of 120 pounds, which indicates that Christine suffered from oliguria and fluid retention.

Plaut et al. 1979 evaluated the incidence of nephrotoxicity among 121 adults in intensive care units with presumed or proven bacterial infections and treated with gentamicin intravenously. Nephrotoxicity occurred with gentamicin during 44/121 (36.3%) treatment courses [22].

Buchholtz et al. conducted a prospective observational cohort study to quantify the nephrotoxic effect of gentamicin in patients with infective endocarditis treated with gentamicin. The primary bacteriological etiologies were as follows: Streptococcus species (37.1%), Staphylococcus aureus (18.2%), and Enterococcus species (16.1%).

A total of 287 (77%) of the patients received gentamicin treatment (median duration, 14 days); dosage was adjusted according to daily serum creatinine and trough serum gentamicin levels. Kidney function was determined by estimated endogenous creatinine clearance (EECC). Statistical correlation between gentamicin and EECC change was analyzed, and the association between mortality and nephrotoxicity was investigated.

In the gentamicin group, the mean EECC change was an 8.6% decrease, but in the no-gentamicin group, the mean change was an increase of 2.3% (P = .05). The decrease in EECC was significantly correlated with the duration of gentamicin treatment: a 0.5% EECC decrease per day of gentamicin treatment (P = .002) [10].

In addition, Nakayama et al. conducted a prospective study in 6 patients who were given intravenous administration of GM (18-42 days in combination with a beta-lactam/carbapenem antibiotic or vancomycin) for the treatment of infective endocarditis. Systemic clearance of GM (CLGM) was reduced significantly (P < 0.05) by 10% from the early to late treatment phase, whereas urinary lipocalin-type prostaglandin D synthase (L-PGDS) excretion showed a significant (P < 0.05) increase (from 7.3 +/- 4.6 to 8.7 +/- 5.0 mg/g creatinine, mean +/- SD) concomitantly. Urinary L-PGDS is used as biomarker for GM-induced renal impairment [23].

Furthermore, Mohammadi-Karakani et al. measured the levels of N-acetyl-beta-D-glucosaminidase (NAG), lactate dehydrogenase (LDH) and alkaline phosphatase (AP) in the urine of 32 children aged 2 months through 2 years, treated with gentamicin and amikacin for suspected infections. Fresh urine before and after drug infusion were obtained on the 1^{st}, 3^{rd}, and 5^{th} days of antibiotic treatment. A statistically significant increase in urinary NAG, LDH, and AP on 5^{th} day was found compared with before gentamicin administration (P < 0.001, P < 0.01, P < 0.05, respectively). The increase in the levels of N-acetyl-beta-D-glucosaminidase (NAG), lactate dehydrogenase (LDH) and alkaline phosphatase (AP) in urine suggests proximal tubular cell damage [12].

Nagai stated that most of the intravenously administered dose of gentamicin is excreted into the urine, whereas some of the aminoglycoside injected (about 10% of the dose) is selectively accumulated in the renal cortex, leading to renal injury. Aminoglycosides are taken up into the epithelial cells of the renal

proximal tubules by an endocytic pathway. Acidic phospholipids, broadly distributed in the plasma membranes in various tissues, were considered to be the binding site of aminoglycosides [13].

Several lines of evidence indicate that free radicals are important mediators of gentamicin (GM) nephrotoxicity and GM increases lipid peroxidation [8, 9, 16, 17, 18, 24-26]. For example, Abdel-Raheem et al. evaluated the nephrotoxicy of gentamicin (GM) in experimental animals. They treated rats with GM (80 mg/kg/d, intraperitoneally) for 7 d and control rats injected with normal saline. Total protein levels were estimated in 24-h urine samples to assess kidney dysfunction.

The rats were sacrificed on the seventh day and kidneys were collected for histopathological studies. Blood urea nitrogen (BUN) and creatinine levels were measured in the blood. Moreover, glutathione (GSH), lipid peroxide (TBARS) levels, superoxide dismutase (SOD) and catalase (CAT) activities were determined in renal tissues.

GM-treated rats showed early kidney dysfunction as urinary total protein, blood urea nitrogen (BUN) and serum creatinine levels were significantly increased. The significant decrease in glutathione (GSH) levels, superoxide dismutase (SOD) and catalase (CAT) activities and increase in lipid peroxide (TBARS) levels, indicated that GM-induced nephrotoxicity was mediated through oxidative stress reactions. Histopathological examination of GM-treated rats revealed degenerative changes in glomeruli and tubules [8].

Lenz et al. also administered gentamicin to rats daily, for 7 days, at 60 mg kg-1 day-1, subcutaneously, twice daily. Conventional clinical chemistry urinalysis showed a significant increase in N-acetyl-beta-D-glucosaminidase (NAG) activity from day 3. At

necropsy on day 9, clear histological damage to the kidney was noted with all animals showing a generally severe nephropathy primarily focused on the proximal convoluted tubules [27].

Furthermore, Stojiljkovi et al. treated rats with gentamicin (GM) daily at a dose level of 100 mg/kg for 8 days. The control rats received 1 ml/day saline intraperitoneally. Histological examinations were done using hematoxylin and eosin, periodic acid Schiff and methenamine silver staining methods. Biochemical analyses were used to determine concentrations of blood urea, serum creatinine, sodium and potassium.

In GM-group rats glomerular basement membrane was diffusely and unequally thickened with polymorphonuclear neutrophils infiltration, while coagulation-type necrosis and vacuolization of cytoplasm of proximal tubules epithelial cells were observed. Blood urea and serum creatinine concentration in GM-group were significantly elevated in comparison with control-group ($p<0,05$) [19].

IV-B. Nephrotoxicity of acyclovir

Christine was treated with acyclovir at a dose level of 800 mg twice per day (39.4 mg/kg per day) for 5 days prior to her death. Acyclovir nephrotoxicity, renal failure, oliguria, anuria, and neurological problems have been described in individuals who were treated with therapeutic doses of acyclovir [28-40]. However, Christine was not monitored for nephrotoxicity during the course of her treatment with acyclovir and other medications that are known to cause kidney problems.

For example, Pacheco et al. evaluated the incidence and outcome of acute renal failure (ARF) in 41 individuals (over 13 years of age) received IV acyclovir for 5 or more days.

When serum creatinine levels, previously in the normal range, increased above 2 mg/dL, the case was considered an ARF. ARF developed in 8 out of 41 individuals (19.5%).

In the ARF cases, after beginning of treatment, the average time for increase of the serum creatinine levels was 4.2 days. Creatinine levels reached their peak in a mean time of 7.1 days (ranging from 3 to 14 days). Recovery of the renal function, evaluated by decrease of the creatinine level, varied from 1 to 7 days (mean of 3.6 days)[37].

In addition, Sawyer et al. evaluated four individuals who experienced five episodes of acute renal insufficiency associated with high-dose (500 mg/m2) intravenous acyclovir administered intravenously as one-hour infusions. Examination of the urinary sediment of three individuals by polarizing microscopy showed birefringent needle-shaped crystals within leukocytes. In the most severely affected individual, a serum creatinine concentration of 8.6 mg/dL developed [39].

Furthermore, Catalano and Conforto described two cases of individuals with normal serum creatinine who developed acute renal failure (ARF) and neurotoxicity after ingesting Valaciclovir (VAL) at the conventional therapeutic dose. VAL is the L-valyl ester of acyclovir.

The first individual was a 77-year-old female admitted to the intensive care unit because of anuria associated with coma and respiratory insufficiency. Her baseline serum creatinine (Scr) was 0.9 mg/dL and increased to 7 mg/dL following four days of treatment with VAL (1 g twice per day). Her urinary output was <100 mL/24 h.

This individual was ventilated and hemodialysis (HD) was started. After 6 days her urinary output increased and dialysis was discontinued. Two weeks after admission, Scr was 1.5 mg/dL, ventilation was discontinued and her consciousness level was normal.

The second individual was a 73-year-old male who developed oliguria and stupor after 4 days of receiving VAL (1 g twice daily). His baseline Scr was 0.7 mg/dL and increased to 5.5 mg/dL. His serum potassium was 6 mEq/L and he was unconscious. After drug withdrawal, the diuresis increased and his consciousness level returned to normal. His Scr reduced to 0.9 mg/dL after 7 days of stopping VAL [29].

Becker et al. also presented a case of an individual who rapidly developed progressive acute renal failure with concomitant mental status changes in the setting of treatment with high-dose parenteral acyclovir. Acyclovir therapy was discontinued and an open renal biopsy was obtained to further evaluate the patient's diminishing renal function. Pathologic examination of the biopsy specimen revealed loss of proximal tubule brush border and dilated proximal and distal tubules with flattening of lining cells and focal nuclear loss. Over the next 4 days, the individual's renal and neurologic levels recovered to their prehospitalization statuses [28].

In addition, De Deyne et al. reported a case of a previously healthy 42 years old man treated by intravenous aciclovir 1g per 8 hours who developed an acute renal failure and an acute confusional state at the end of the treatment. Renal function and neurologic status improved rapidly with increased hydration and stopping the antiviral therapy [31].

Furthermore, Vachvanichsanong et al. reported a case of a 9-year-old boy developed acute renal failure following intravenous acyclovir (30 mg/kg per day) administered for 6 days to treat herpetic encephalitis. Acyclovir was discontinued and conservative treatment and hydration were carried out. The kidney function returned to normal within 1 week [40].

Section V. The likely causes of Christine's acute left ventricular heart failure and severe pulmonary edema

Dr. Posey stated that Christine's pericardial sac and left chest cavity contained 100 mL and 200 mL of clear light brown serious fluid, respectively. She also had severe pulmonary edema. The weights of her right and left lung were 1319 and 1307 g, respectively.

A chest X-ray performed on December 18, 2008 did not show that Christine had abnormal fluid in her pericardial sac and left chest cavity or pulmonary edema. Christine developed acute renal failure as a result of receiving medications and calcium on December 18-26, 2008 (Section IV). It led to the development of acute left ventricular heart failure and pulmonary edema as described below.

V- A. Signs and causes of Christine's acute left ventricular heart failure

Christine's pericardial sac and left chest cavity contained 100 mL and 200 mL of clear light brown serious fluid, respectively. Normally, the pericardial sac contains up to 30 ml of clear fluid. In left-sided heart failure, transudate accumulates within the pleural spaces frequently, particularly, on the left side, producing a gross pleural effusion [5]. No abnormal fluid was found in Christine's right chest cavity and abdominal cavity.

Posey examined Christine's heart grossly and it appeared normal. Her heart weighted 329 g. In the female, the average weight of the heart is 250 to 300 g [5]. His microscopic examination of the H & E stained sections of Christine's heart demonstrated mild interstitial edema, but otherwise it was unremarkable.

There was no evidence of recent or remote myocardial infarct or damage observed in Christine's heart and the sinoaterial node was unremarkable. A blood test performed at 2

years prior to Christine's death showed that she had a very low risk for cardiovascular disease (Section I-C).

A chest X-ray performed on December 18, 2008, prior to Christine's treatment with medications and calcium did not show that she had pulmonary edema and abnormal fluid in her pericardial sac and left chest cavity. Christine developed acute renal failure as a result of the medications and calcium received on December 18-26, 2008 (Section IV). It led to development of hypocalcaemia, metabolic problems, and acute left ventricular heart failure.

The microscopic examination of the H & E stained sections of Christine's kidneys revealed the presence of changes consistent with acute tubular necrosis in both kidneys. Acute tubular necrosis can produce a variety of clinical consequences affecting the entire body, including hyperkalemia, acidosis, hypocalcemia, and anemia, as well as various cardiovascular, neurologic, and gastrointestinal problems [41, 42].

The ionized calcium concentration in blood is maintained within narrow limits by a complex hormonal system that includes parathyroid hormone (PTH) and vitamin D. The kidney plays a pivotal role in the physiologic action of PTH, as this peptide hormone increases tubular calcium reabsorption, decreases tubular phosphate re-absorption, and stimulates the renal 25-hydroxy-1-hydroxylase to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the hormonal form of the vitamin that stimulates intestinal calcium absorption. Inherited and acquired disorders of tubular function and acute and chronic renal failure may disturb normal renal handling of calcium and phosphorus and the hydroxylation of 25-hydroxyvitamin D [43].

Left ventricular heart failure has been reported in individuals suffering from severe hypocalcaemia and their heart condition improved dramatically after receiving treatment for hypocalcaemia [44-57].

For example, Kazmi and Wall evaluated a case of a 71-year-old man presented with acute pulmonary edema related to new onset of severe left ventricular dysfunction (ejection fraction, 30%). His symptoms did not improve after emergency therapy with diuretics and dobutamine. He was noted to be severely hypocalcemic (5.5 mg/dL) and subsequently showed dramatic improvement in symptoms and ejection fraction (58%) with correction of hypocalcemia with intravenous calcium and calcitriol replacement [48].

In addition, Schär et al. reported the case of a 50-year-old female in whom the connection between hypocalcemia and heart failure was not made until a second hospital admission for left ventricular failure. Under appropriate calcium supplementation the symptoms were relieved within 2 days and the woman remained well thereafter [57].

Mathieu et al. 2005 also reported a case of a young individual with acute left ventricular failure due to severe hypocalcaemia secondary to the intestinal malabsorption of calcium due to inflammatory bowel disease. The hemodynamic deterioration occurred very rapidly in this case. A total reversal of the individual's heart condition was accomplished within one week following correction of the hypocalcaemia [53].

Furthermore, Avsar et al. described a case of 40-year-old woman who had severe heart failure due to hypocalcemia. Echocardiography showed a large left ventricle with very low ejection fraction of 25% and moderate mitral regurgitation. After supplementation of calcium and vitamin D, her clinical situation and hemodynamics improved rapidly. At 15 months, myocardial impairment resolved fully [45].

Arı et al. also described a case of 27-year-old man who developed severe heart failure as a result of severe hypocalcemia. Echocardiography showed left ventricular dilatation, global hypokinesia (ejection fraction 25%), and mitral and tricuspid regurgitation of grades 3 and 2, respectively. After calcium and vitamin D supplementation, his symptoms showed rapid improvement. At nine months, myocardial dysfunction improved fully [44].

In addition, Mönig et al. evaluated a case of a 25-year-old man hospitalized because of dyspnea and retrosternal pain. There were clinical and radiological signs of severe left ventricular failure, which within a few hours necessitated artificial ventilation. His severe left ventricular failure did not respond adequately to the usual therapeutic measures including artificial ventilation and catecholamines.

On admission, his serum calcium concentration was 1.5 mmol/L. A cumulative dose of about 50 mmol calcium was administered intravenously over 10 days. Marked improvement in myocardial function became apparent at a calcium concentration of about 1.8 mmol/L. Lasting correction of the hypocalcaemia was achieved with 0.5 g calcium three times daily by mouth and 0.5 mg/day dihydrotachysterol [54].

Furthermore, Charniot et al. reported a case of 58-year-old woman admitted to the hospital because of cardiac failure. Her ECG showed sinus tachycardia with a long QT interval (560 mm) and a dilated hypokinetic cardiomyopathy with a left ventricular ejection fraction of 20%. The aetiological investigation showed severe hypocalcaemia (0.66 mmol/L) and treatment led to correction of her cardiac disease within weeks [47].

Massing et al. also reported a case of 28-year-old woman with acute left ventricular failure associated with severe hypocalcaemia (1.7 mmol/l). The echocardiographic appearances were those of dilated and globally hypokinetic cardiomyopathy with a

severely depressed left ventricular ejection fraction (23%). Hemodynamic improvement was only obtained by the association of calcium supplements and vitamin D derivatives to conventional treatment [52].

V- B. Signs and causes of Christine's acute pulmonary edema

Christine suffered from severe pulmonary edema. Her total lung weight was 2626 g, which is 750% of the average normal lung weight. The average normal weight of human lung is 300 to 400 g [5]. Posey's microscopic examination of the H & E stained tissue sections of Christine's lungs demonstrate severe congestion and edema. All sections from both lungs showed marked alveolar distention by frothy eosinophilic proteinaceous exudates.

A chest X-ray performed on December 18, 2008, which is 9 days prior to Christine's death, did not show that she had severe pulmonary edema. She had patchy interstitial infiltrate in both mid and lower lung fields. Her pulmonary vascularity was within normal limits and her mediastinum was midline and normal in contour.

Christine's pulmonary edema resulted as a consequence of her left-sided heart failure. The distant effects of left-sided failure are manifested most prominently in the lungs. In left-sided heart failure, transudate also accumulates within the pleural spaces, particularly on the left side [5]. Christine had 200 mL of pleural fluid in the left side.

Pulmonary edema has been reported in individuals who are suffering from heart failure [48, 58-73]. In heart failure, there is an increase in pulmonary venous and capillary pressure and therefore in the forces moving fluid into the interstitium of the lung. Simultaneously the interendothelia junction stretch is are widened, allowing the increased movement of both fluid and macromolecules into the interstitium.

When critical elevations in interstitial pressure are reached or increased pressure is prolonged that the tight junctions between alveolar lining epithelial cells break and alveolar edema results [5]. Posey's microscopic examination of section of Christine's lung stained with PSA showed evidence of early onset of diffuse alveolar damage characterized by widening and edema of the alveolar septae.

Section VI. The likely causes of the benign lesions observed in Christine's thyroid gland and liver

Dr. Posey examined Christine's thyroid glands and liver grossly and microscopically. Benign lesions were the only abnormality observed. These were a benign microscopic follicular adenoma in the thyroid glands and a benign focal nodular hyperplasia (8 x 5.5 x 3.5 cm) in the liver. The clinical data, studies, and observations described below indicate that medications given to Christine on December 18-26, 2008 caused her thyroid and liver lesions.

VI-A. Causes of Christine's benign microscopic thyroid adenoma

The following clinical data, studies, and observations indicate that medications given to Christine on December 18-26, 2008 and changes induced in the liver are the likely causes for Christine's thyroid problem:

1) Blood tests performed at 13.5 and 24.5 months prior to Christine's death showed that her serum TSH, T3, and T4 levels were within the normal range and she did not have thyroid problems. In addition, her blood tested negative for autoimmune disease (Section I-B).

2) Dr. Posey examined Christine's pituitary glands grossly and microscopically and it appeared normal. It indicates that she did not have pituitary problem leading to thyroid problem.

3) Christine's weight on December 18, 2007 and October 19, 2008 was 120 pounds. People suffering from hypothyroidism usually gain weight and from hyperactive thyroid lose weight.

4) It has been reported that medications can interfere with the functions of the thyroid glands [74-76]. For example, large doses of corticosteroids produce reductions in total T3 levels [74]. Christine was treated with high therapeutic dose of corticosteroids during the 9 days prior to her death (Table 10).

In addition, liver is involved in the metabolism of a large number of circulating hormones and liver diseases are often associated with hormonal disorders [77]. It is possible that the focal hyperplasia observed in Christine's liver affected the metabolism of the thyroid hormones and led to thyroid problem.

VI-B. Causes of Christine's benign focal nodular hyperplasia

The following clinical data, studies, and observations indicate that medications given to Christine on December 18-26, 2008 caused her benign focal lesion in the liver:

1) Blood tests performed at 13.5 and 24.5 months prior to Christine's death showed that her liver functions test results were within the normal range and she did not suffer from liver problems (Section I-D).

2) Christine was treated with high therapeutic doses of antibiotics, antiviral, and antifungal drugs during the 9 days prior to her death (Table 10). Focal nodular hyperplasia (FNH) in liver has been reported following ingestion of various medications and chemical agents. Its development may be related to the vascular damage and ischemia induced by chemical agents [78-82].

For example, Bazlul Karim et al. reported case of a young girl who developed FNH in liver following ingestion of anti-tuberculosis drugs for the treatment of her abdominal tuberculosis [78]. In addition, Joyner et al. reported 3 cases of children who developed FNH after undergoing anti-neoplastic therapy for non-hepatic primary tumors [79].

Section VII. The likely causes of Pneumocystis jiroveci growth observed in Christine's organs at the time of autopsy

Dr. Posey examined Christine's lymphoid organs and bone marrow grossly and microscopically and appeared normal (Table 13). However, his microscopic examination of the H & E stained sections of Christine's organs revealed the presence of Pneumocyte jiroveci in sections of the lung, liver, pancreas, kidneys, and bone marrow (Table 14). The presence of P. jiroveci in Christine's lungs and other organs was not associated with any pathological lesion as described in Table 14.

P. jiroveci is found in the respiratory system of healthy individuals and treatment with therapeutic doses of corticosteroids for a significant time promote it's growth. The following clinical observations and studies indicate that the growth of P. jiroveci in Christine's tissues resulted from her treatment with corticosteroids during the 9 days prior to hear death (Table 10).

1) Blood analyses performed during the 2 years prior to Christine's death revealed that a) her hematology values were within the normal range and she did not suffer from anemia or hematological abnormalities (Table 1); b) Christine's blood white blood cells and differential counts were within the normal range and she did not suffer from infections, leukocytopenia, or lymphocytopenia (Table 2).

2) Posey's gross and microscopic evaluation of Christine's thymus, spleen, lymph nodes, and bone marrow revealed that these organs were normal (Table 13), which indicates that Christine was not suffering from immune deficiency problems. P. jiroveci is a fungus found in the respiratory system of healthy individuals and causes interstitial pneumonia only in people suffering from severe immune deficiency.

3) It has been widely reported that the treatment of individuals with high therapeutic doses of corticosteroids for a significant time lead to the growth of P. jiroveci in the lungs [5, 83-91]. Christine was treated with significant doses of corticosteroids during the 9 days prior to her death (Table 10), which promoted the growth of P. jiroveci in her lungs.

4) P. jiroveci has been known to cause interstitial pneumonia in individuals suffering from severe immunosuppression [5, 84, 90, 92]. Christine did not have interstitial pneumonia and the edema observed in her lungs resulted from her heart and renal failure induced by medications.

5) P. jiroveci was observed in Christine's lungs and 5 other organs without causing any reactions (Table 14). It may indicate that the growth of P. jiroveci occurred after death. Christine died on December 27, 2008 and her autopsy was completed on January 12, 2009.

Table 13. Posey's gross and microscopic descriptions of Christine's lymphoid organs and bone marrow

Organs	Gross	Microscopic (H & E stained section)
Thymus	• Normal for age	
Spleen	• Unremarkable dark red-purple • weighted 189 g	• Mildly congested
Lymph nodes	• Normal size and consistency	• A section of lymph node was unremarkable.
Bone Marrow*	• Red and moist	• Demonstrated normal trabeculae and appeared to have normal cellularity.

Table 14. Locations of Pneumocyte jiroveci observed in Christine's organs

Organs	Locations of Pneumocyte jiroveci
Lung	• Large number of small uniformly round to oval fungal organisms, P. Jroveci were seen in the frothy exudates, separately within the alveoli, within the lung parenchyma, and in occasional vascular spaces. • These organisms were identified on Gomori methenamine silver (GMS) preparation. • The PAS preparation outlined the P. jiroveci organisms and showed no evidence of hyaline membrane deposition. • No evidence of either herpes viral infection or infection by cytomegalovirus was observed.
Liver	• The uninvolved liver was unremarkable, except for mild sinusoidal congestion and occasional P. jiroveci were seen on the H & E preparation and confirmed on the GMS stain.
Pancreas	• The pancreas was autolyzed, but P. jiroveci were seen on the GMS preparation.
Spleen	• Occasional P. jiroveci noted in the spleen and confirmed on the GMS preparation.
Kidneys	• Dull gray amorphous P. jiroveci was noted in both the glomeruli and tubules, and their presence was confirmed with the GMS preparation. • PAS discloses no abnormal deposits within the glomeruli.
Bone marrow	• Occasional P. jiroveci were seen in bone marrow and confirmed on the GMS preparation.

Section VIII. Conclusions

Christine Maggiore was diagnosed with pneumonia on December 18, 2008 and was treated with antibiotics (Gentamicin, Rocephin, Azithromycin), Acyclovir, Fluconazole and corticosteroids. She also received Meyer's cocktail, vitamin C, and calcium IV. She died on December 27,2008. The clinical data and observations and medical studies described in this report indicate the following:

1) Christine developed acute renal failure as a result of the medications received during the 9 days prior to her death as described below:

a) Christine was treated with high therapeutic doses of gentamicin (600 mg/day) for 9 days prior to her death and gentamicin is known to cause tubular necrosis in individuals treated with similar doses.

b) She was treated with Rocephin (ceftriaxone) at 1 g/day twice daily and calcium solution IV for several days prior to her death. The treatment of ceftriaxone with calcium is contraindicated. In June 2007, the US FDA advised that in patients of all ages, calcium-containing solutions should not be administered simultaneously or within 48 hours of the last ceftriaxone dose. The FDA received reports on neonatal and infant deaths associated with ceftriaxone-calcium precipitation in the lungs and kidneys.

c) Christine was treated with high therapeutic doses of acyclovir (800 mg twice daily) for 5 days prior to her death and acyclovir has known to cause kidney damage in individuals treated with similar doses.

Christine's autopsy weight was 145 pounds, which is 20.8% higher than her normal weight of 120 pounds measured during the 2 years prior to her death. It indicates that she suffered from fluid retention due oliguria/anuria caused by renal failure. No blood and

urine tests were performed during the 9 days prior to Christine's death to monitor for drugs toxicity.

Blood and urine tests performed on December 15, 2006 and November 9, 2007 showed that Christine's kidneys were working fine. She was not suffering from electrolytes imbalance, urinary tract infection, or kidney problems.

2) Christine's acute renal failure led to development of acute left ventricular heart failure. Acute tubular necrosis usually produce a variety of clinical consequences affecting the entire body, including hyperkalemia, acidosis, hypocalcemia, and anemia, as well as various cardiovascular, neurologic, gastrointestinal problems, and death.

Christine's pericardial sac and left chest cavity contained 100 mL and 200 mL of clear light brown serious fluid, respectively. Normally, the pericardial sac contains up to 30 ml of clear fluid. In left-sided heart failure, transudate accumulates within the pleural spaces frequently, particularly, on the left side, producing a gross pleural effusion. A chest X-ray performed on December 18, 2008, prior to Christine's treatment with medications and calcium did not show that she abnormal fluid in her pericardial sac and left chest cavity. In addition, a blood test performed at 2 years prior to Christine's death showed that she had a very low risk for cardiovascular disease.

3) Christine suffered from severe pulmonary edema due to her left ventricular heart failure. Her total lung weight was 2626 g, which is 750% of the average normal lung weight. The average normal weight of human lung is 300 to 400 g. A chest X-ray performed on December 18, 2008, prior to Christine's treatment with medications and calcium did not show that she had pulmonary edema and abnormal fluid in her pericardial sac and left chest cavity.

In heart failure, there is an increase in pulmonary venous and capillary pressure and therefore in the forces moving fluid into the interstitium of the lung. Simultaneously the interendothelia junction stretch, are widened, and allow the increased movement of both fluid and macromolecules into the interstitium. When critical elevations in interstitial pressure are reached or increased pressure is prolonged that the tight junctions between alveolar lining epithelial cells break, alveolar edema results.

4) The growth of P. jiroveci observed in Christine's lungs and other tissues resulted from her treatment with corticosteroids during the 9 days prior to hear death as indicated by the following clinical observations: a) Dr. Posey examined Christine's lymphoid organs and bone marrow grossly and microscopically and appeared normal. b) The presence of P. jiroveci in Christine's lungs and other organs was not associated with any pathological lesion. P. jiroveci is known to cause interstitial pneumonia in individuals suffering from severe immunosuppression. Christine did not have interstitial pneumonia and the edema observed in her lungs resulted from her heart and renal failure induced by medications. c) P. jiroveci is found in the respiratory system of healthy individuals and treatment with therapeutic doses of corticosteroids for a significant time promote its growth. d) Blood analyses performed during the 2 years prior to Christine's death revealed that her hematology values and white blood cells and differential counts were within the normal range.

5) Medications given to Christine on December 18-26, 2008 are the likely causes for the benign lesions observed in her thyroid gland and liver.

6) Christine did not suffer from any AIDS indicator illness during the 2 years prior to her death and at the time of her death. It has been reported that Christine's serum was tested positive for HIV with subsequent testing indeterminate in the 1990s. The clinical findings in Christine clearly challenge the clinical and the scientific validity of her HIV test.

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