Fanconi syndrome in lymphoma patients: report of the first case series

Jill Vanmassenhove1, Marion Sallée1, Philippe Guilpain2, Raymond Vanholder3, Alexandra De Potter4, Louis Libbrecht4, Felipe Suarez5, Olivier Hermine5 and Fadi Fakhouri1

1Nephrology Department, Université Paris Descartes, AP-HP, Hôpital Necker, Paris, France, 2Internal Medicine Department, Hôpital Cochin, Paris, France, 3Nephrology Section, Department of Internal Medicine, University Hospital, Ghent, Belgium, 4Pathology Department, University Hospital, Ghent, Belgium and 5Haematology Department, Hôpital Necker, Paris, France

Correspondence and offprint requests to: Fadi Fakhouri. E-mail: fadi.fakhouri@chu-nantes.fr

Abstract

Background. Fanconi syndrome (FS) is a generalized transport defect in the proximal renal tubule leading to renal losses of phosphate, calcium, uric acid, bicarbonates as well as glucose, amino acids and other organic compounds. It is caused by inherited or acquired disorders including low mass or high mass multiple myeloma.

Objectives. To report the first case series of patients with lymphoma and FS.

Design, setting, participants, and measurements. Patients with lymphoma and FS were identified in the nephrology department of two teaching hospitals in Paris, France and Ghent, Belgium. FS was defined by the presence of at least three out of the four following criteria: hypophosphataemia, metabolic acidosis, normoglycaemic glucosuria and hypokalaemia. Patients files were reviewed and relevant data were collected.

Results. Eight patients with lymphoma and FS were identified. In six patients, the lymphoma was of the acute T cell leukaemia/lymphoma (ATLL) type, related to human T cell lymphotropic virus 1 (HTLV-1) infection. In all patients, FS was severe requiring supplementation. A kidney biopsy performed in a patient with post-transplantation primary renal lymphoma disclosed intense proximal tubule infiltration by lymphomatous cells. In one patient with ATLL, FS features regressed following the successful treatment of lymphoma.

Conclusion. Patients with lymphoma require careful monitoring for features of FS; lymphoma should also be added to the spectrum of disorders associated to FS. Prospective studies are needed to ascertain the implication of HTLV-1 in the genesis of FS.

Keywords: Fanconi syndrome; HTLV-1; lymphoma

Introduction

Fanconi syndrome (FS) is a generalized transport defect in the proximal renal tubule leading to renal losses of phosphate, calcium, uric acid, bicarbonates as well as glucose, amino acids and other organic compounds.

FS may be caused by various inherited diseases (mitochondrial cytopathies, cystinosis) or acquired, mainly following the use of exogenous agents (ifosfamide, tenofovir, etc.) [1]. It has also been reported in the setting of low mass or high mass multiple myeloma and has been associated in some cases to the accumulation of light chain crystals in the renal proximal tubular cells [2,3].

Constitutional or acquired mitochondrial dysfunction is another leading cause of dysfunction of the proximal convoluted tubule in which multiple absorption activities require high-level energy input. The pathological mechanisms underlying FS have not been clearly elucidated, although experimental models showed that defective luminal entry, excessive backleak or interference with basolateral NaK-ATPase activity may be involved [1].

We report the first case series of FS in eight patients with lymphoma and discuss the putative mechanisms leading to the coexistence of these two entities.

Case Reports

Eight patients with lymphoma and FS seen in the nephrology departments in two teaching hospitals in France (Hôpital Necker, Paris) and Belgium (University Hospital, Ghent) were identified. FS was defined as the presence of at least three out of the four following criteria: (i) hypophosphatemia [phosphatemia < 0.7 mmol/l (<2.17 mg/dl)], (ii) metabolic acidosis (total plasma CO2 < 20 mmol/l), (iii) normoglycaemic glucosuria and (iv) hypokalaemia (<3.5 mmol/l).

Patients with hypercalcaemia were excluded since hypercalcaemia per se may induce tubulopathy.

Patients’ clinical and biological characteristics at the time of FS diagnosis are summarized in Table 1. All patients were in an acute phase of lymphoma (initial diagnosis or relapse) at the time of diagnosis of FS. The lymphoma was of the acute T cell leukaemia/lymphoma (ATLL) type, related to human T cell lymphotropic virus 1 (HTLV-1) infection in six patients out of eight (patients 1–6). The six patients with FS and ATLL were identified among a cohort of 28 patients (incidence 21%) with ATLL seen in the haematology department of Hôpital Necker between 1998 and 2008.
Fanconi syndrome in lymphoma patients: report of the first case series

Table 1. Clinical and biological features of eight patients with lymphoma and Fanconi syndrome

<table>
<thead>
<tr>
<th>Patient/sex</th>
<th>1/Male</th>
<th>2/Female</th>
<th>3/Male</th>
<th>4/Male</th>
<th>5/Male</th>
<th>6/Female</th>
<th>7/Female</th>
<th>8/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65</td>
<td>35</td>
<td>52</td>
<td>41</td>
<td>44</td>
<td>51</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Time between haemopathy and FS (months)</td>
<td>9</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.1</td>
<td>2.8</td>
<td>3.3</td>
<td>2.7</td>
<td>3.2</td>
<td>2.8</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Serum magnesium (mmol/l)</td>
<td>0.71</td>
<td>0.65</td>
<td>0.65</td>
<td>0.62</td>
<td>0.48</td>
<td>0.55</td>
<td>1.08</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l)</td>
<td>0.28</td>
<td>0.35</td>
<td>0.39</td>
<td>0.33</td>
<td>0.49</td>
<td>0.28</td>
<td>0.36</td>
<td>0.33</td>
</tr>
<tr>
<td>Total CO2 (mmol/l)</td>
<td>14.8</td>
<td>17.3</td>
<td>12.3</td>
<td>24.8</td>
<td>15.5</td>
<td>16.5</td>
<td>14.6</td>
<td>13</td>
</tr>
<tr>
<td>Puria/cruria (g/mmol)</td>
<td>0.27</td>
<td>0.43</td>
<td>0.05</td>
<td>0.09</td>
<td>0.7</td>
<td>0.32</td>
<td>0.42</td>
<td>0.28</td>
</tr>
<tr>
<td>Glucosuria mmol/24 h</td>
<td>42.4</td>
<td>46.2</td>
<td>42.5</td>
<td>81</td>
<td>115</td>
<td>94</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>kaliuria mmol/24 h</td>
<td>46.2</td>
<td>41.7</td>
<td>81</td>
<td>42.5</td>
<td>1.7</td>
<td>22</td>
<td>24.4</td>
<td>72</td>
</tr>
<tr>
<td>TmPFGR (ml/min/1.73 m²)</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

As drugs, especially antiretroviral and anti-cancer agents, are a leading cause of FS, all treatments received by the eight patients at the time of FS diagnosis were carefully reviewed. In all patients, FS was present before the start of specific chemotherapy.

Among the six patients with HTLV-1-related ATLL, two received long-term antiretroviral therapy that has been linked in rare instances to FS. In patient 2, abacavir and lamivudine [4] had been started 3 years before the diagnosis of FS. No features of proximal tubulopathy had been noted until the occurrence of lymphoma. In patient 4, treatment with didanosine and stavudine [5,6] was started concomitantly to the diagnosis of FS.

Some reports have suggested an association between proximal tubulopathy and aminoglycosides [7] mainly for high doses (up to 10 g) and for extended duration (>6 days). All patients had received no aminoglycosides or moderate doses of these antibiotics for relatively short periods.

As drugs, especially antiretroviral and anti-cancer agents, are a leading cause of FS, all treatments received by the eight patients at the time of FS diagnosis were carefully reviewed. In all patients, FS was present before the start of specific chemotherapy.

Among the six patients with HTLV-1-related ATLL, two received long-term antiretroviral therapy that has been linked in rare instances to FS. In patient 2, abacavir and lamivudine [4] had been started 3 years before the diagnosis of FS. No features of proximal tubulopathy had been noted until the occurrence of lymphoma. In patient 4, treatment with didanosine and stavudine [5,6] was started concomitantly to the diagnosis of FS.

Some reports have suggested an association between proximal tubulopathy and aminoglycosides [7] mainly for high doses (up to 10 g) and for extended duration (>6 days). All patients had received no aminoglycosides or moderate doses of these antibiotics for relatively short periods. Patient 1, 5 and 6 had FS before the start of treatment with aminoglycosides. Patient 3 received gentamycin (total dose 1 g over 4 days), and patient 4 received gentamycin (0.4 g over 3 days) and amikacin (2.7 g over 3 days). FS was diagnosed 2 and 3 days after the start of aminoglycosides.

### Discussion

Renal involvement in the setting of the wide spectrum of Hodgkin and non-Hodgkin lymphomas is well documented and includes a heterogeneous range of nephropathies: renal parenchymal infiltration by primary and non-primary renal lymphomas [8,9], atypical membranoproliferative, cryoglobulinemic and immunotactoid glomerulonephritis [10,11], amyloidosis [12], minimal chain disease [13] and acute tubulointerstitial nephritis in the setting of lymphoma-associated haemophagocytic syndrome [14].

To the best of our knowledge, FS has been previously reported in one single case of Burkitt's lymphoma infiltrating the kidney [15]. Herein, we report the first case series of lymphoma patients presenting with FS. All patients had overt severe FS requiring massive supplementation. Other causes of FS, mainly drugs, have been excluded. Moreover in patient 1, the evolution of FS paralleled the evolution of...
lymphoma. This finding, along with the intense renal tissue infiltration of proximal tubular cells by lymphomatous cells in patient 8, pleads for a causal relation between lymphoma and FS. Finally, the incidence of FS in lymphoma patients is probably underestimated as clinicians usually do not monitor patients systematically for the presence of FS features. However, the most striking observation in our report is the association of FS to HTLV-1 ATLL in six out of eight patients, although ATLL is a rather uncommon disorder.

HTLV-1 is a retrovirus, endemic in southern Japan, the Caribbean, South America, the Middle East and central and southern Africa [16]. Even though the majority of HTLV-1 infected patients remain asymptomatic, HTLV-1 is associated with severe diseases: neoplastic diseases (ATLL), inflammatory syndromes (HTLV-1-associated myelopathy/tropical spastic paresis, uveitis, etc.) and opportunistic infections (*Strongyloides stercoralis* hyperinfection, etc.) [17].

The main host cells infected by HTLV-1 *in vivo* are CD4+ and CD8+ T cells. HTLV-1 enters and infects T lymphocytes via the GLUT-1 receptor and neuropilin 1 [18]. Renal involvement in the setting of HTLV-1 infection remains ill defined. Acute renal in the setting of hypercalcaemia due to secretion of parathyroid hormone (PTH)-related protein [19], membranoproliferative glomerulonephritis and thrombotic microangiopathy have been rarely reported [20]. Two putative pathogenic mechanisms may underlie the association of FS with lymphoma in our patients. Firstly, infiltration of renal parenchyma by lymphomatous cells (as in patients 1 and 8) may explain the occurrence of FS in our patients. However in our series, only patient 8 presented with impaired kidney function, whereas lymphomatous infiltration of the kidney usually leads to renal insufficiency [21]. Renal lymphomatous infiltration in our patients may not be the predominant pathogenic mech-
Fanconi syndrome in lymphoma patients: report of the first case series

anism underlying FS. Intrarenal cytokine synthesis induced by lymphomatous cells may lead to proximal tubular toxicity. Moreover, one cannot exclude that some peculiar antigens expressed by proximal tubular cells may drive a specific lymphoma cell reaction directed against proximal tubule. The presence of proximal tubular cell infiltration by lymphomatous cells in the kidney biopsy performed in patient 8 suggests such mechanism. Secondly, glucose transporter-1 (GLUT-1), a member of the family of glucose transporters and a HTLV-I receptor, is expressed on the basolateral membrane of renal proximal tubule, a major site of glucose reabsorption in the kidney [22]. Thus, HTLV-I virions, in the setting of high viral load (e.g. relapse of ATLL), may enter the proximal tubular cells via the GLUT-1 receptor and then spread within the renal parenchyma through cell–cell contact. Interestingly, one of the HTLV-I main proteins, p13(II), is targeted to mitochondria and disrupts mitochondrial function [23], which might be a mechanism leading to mitochondrial dysfunction in proximal tubular cells and hence to FS.

One cannot exclude that the kidney may in some instances represent a sanctuary and replication site for HTLV-1. Although CD4+ T cell compartment appears to be the most important compartment for HTLV-1 persistence in the organism, animal models have shown a broad in vivo tropism of HTLV-I. In rabbit, rat and mouse models of persisted HTLV-1 infection, the virus was detected in a large spectrum of haematopoietic cell types and non-haematopoietic tissues, including brain, lung and most interestingly the kidney [24–27].

The route of HTLV-1 spreading remains controversial. Because cell-free HTLV-I cannot efficiently infect T cells in vitro, it has been widely believed that transmission of HTLV-I is qualitatively different from that of most retroviruses with cell–cell contact between the infected and uninfected cells being the major route of viral transmission in vivo [28,29]. However, a recent publication has shown that HTLV-1 is not poorly infectious, and the mechanism of HTLV-1 transmission is similar to that of other retroviruses [30].

Whatever the pathogenic mechanism, it remains unknown why a minority of patients disclose renal infiltration by lymphoma and FS. Peculiar characteristics of adherence and chemoattractant molecules on proximal tubular and/or lymphomatous cells may underlie these events.

In conclusion, patients with lymphoma require careful monitoring for features of FS. Lymphoma, even if not associated with light chain release, should be added to the spectrum of disorders associated to FS, and patients presenting with FS should be screened for lymphoma when other FS causes have been ruled out. Prospective studies are needed to ascertain the implication of HTLV-I in the genesis of FS.

Conflict of interest statement. None declared.

References

MEFV gene compound heterozygous mutations in familial Mediterranean fever phenotype: a retrospective clinical and molecular study

Ahmet Okay Caglayan¹, Fatma Demiryilmaz¹, Isilay Ozyazgan¹ and Hakan Gumus²

¹Department of Medical Genetics, Kayseri Education and Research Hospital, Kayseri, Turkey and ²Department of Pediatrics, Kayseri Education and Research Hospital, Kayseri, Turkey

Correspondence and offprint requests to: Ahmet Okay Caglayan; E-mail: aocaglayan@erciyes.edu.tr

Abstract

Background. Familial Mediterranean fever (FMF) is an autosomal-recessive inherited inflammatory disease caused by mutations in the MEFV gene that encodes pyrin/marenostatin. It is characterized by recurrent short episodes of fever, abdominal pain and serositis affecting mainly Mediterranean and Middle Eastern populations. We determined the frequency of the compound heterozygous mutations which has been rarely reported. The present study not only investigated clinical features of child-onset FMF patients with compound heterozygous mutations but also determined whether there is a phenotype–genotype correlation in the same patient population.

Methods. The medical records of 66 heterozygous patients with FMF were retrospectively reviewed and assessed. Patients were investigated regarding the mutation type, clinical characteristics at the time of inflammatory attacks such as fever, abdominal pain, arthritis, chest pain, erysipelas-like erythema and oedema, epidemiological data, consanguinity, severity score and family history of FMF and amyloidosis.

Results. The most frequent mutation was M694V, identified in 32% of the alleles examined, followed by E148Q in 20.6%, V726A in 17% and M680I in 14.5%, respectively. Consequently, we determined that P369S (n = 10; 8%) was the most frequent rare mutation in Turkish FMF patients. Frequency of the other rare mutations were R761H (3%), F479L (3%), A744S (1.5%) and K695R (0.7%). Fever was seen in 96.5%, abdominal pain in 98.5%, arthralgia in 85%, chest pain in 45.5% and erysipelas-like lesions in 23%. None of these patients had amyloidosis, but 16 had a family history of chronic renal failure, 44% had vomiting and 35% had diarrhoea during the attack. Although regular colchicine treatment was effective in 83% of the patients, the percentage of patients that did not start colchicine therapy was 18%. In addition, the patients were divided into four groups according to the presence of the mutation types and we compared genotype–phenotype correlations.

Conclusions. We suggest that regular colchicine therapy may be administered to symptomatic patients with MEFV gene compound heterozygous mutations, regardless of the mutation type.

Keywords: compound heterozygous; genetics; MEFV gene

Introduction

Familial Mediterranean fever (FMF) is an autosomal-recessive inherited disease. It affects mainly Mediterranean and Middle Eastern populations, including Turks, Jews, Armenians and Arabs. It is characterized by recurring short episodes of fever, abdominal pain and serositis. Reactive AA amyloidosis frequently occurs in patients with this disease and the prognosis is determined by the complication of AA amyloidosis. There is ethnic variability in the prevalence of amyloidosis; the latter occurs in 37% of Sephardic Jews, 27% of non-Ashkenazi Jews, 12% of Turks, 24% of Armenians and 1–2% of Armenians living in the United States [1]. In untreated Jewish patients of North Af-