Paget’s disease population analysis within Rheumatology Outpatient of the ASL of Biella (Piedmont Region, Italy)

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Summary

The Ambulatory of Biella is the only service of Rheumatology of the Biella area. The Paget’s disease is the 0.5% and appears to be representative of the territory of Biella. We evaluated the pagetic locations, disease activity and quality of life, the presence of gene mutation and frequency of comorbidities and therapeutic efficacy. Patients with active disease were treated with intravenous bisphosphonate therapy and investigated in relation to the side effects: flu-like syndrome and therapeutic efficacy by ALP and scintigraphy. 15 out of 20 patients analyzed resulted as the only pagetic location the pelvic bone. Treatment with bisphosphonates has led to remission of disease: normalization of ALP values in 90%, documented by the scintigraphy of control. In the 86% of cases it was not necessary to make a second infusion, even 3 years after the first administration. In only two cases was carried out another infusion for the persistence of pain, despite levels of ALP prove the rule, in such cases, the scintigraphy can showed uptake of the sites involved. Bone scintigraphy is more sensitive and specific of ALP in determining disease activity and should be used in cases of doubt of retreatment. 53% of cases showed as side effect a flu-like syndrome; 6 months after infusion secondary hyperparathyroidism in 46% of cases. SQSTM1 mutation was positive in two patients originating from Veneto and Sardinia, but in no patients in Biella. The presence of two aggregations family suggesting other mutations in the Biella population.

KEY WORDS: Paget’s disease; zoledronate; SQSTM1 mutation; flu-like syndrome.

Introduction

The Rheumatology poliambulatory of Biella is the only service that takes care of rheumatic diseases in the province. The town of Biella and its province extending over a territory conformation predominantly mountainous place in the Northern Piedmont region, extending from West to East between the provinces of Valle d’Aosta (North-West), Turin (South) and Vercelli (East). The province of Biella is composed of 82 municipalities and has a catchment area of 186,000 inhabitants: 5.6% of these are immigrants residing in the city of Biella (45,600 inhabitants). The population is divided into 47.8% male and 52.5% female according to the database of 2010 BDDE (Demographic Evolutionary Database). The population older than 60 years is 32% of the total population (59,500 people) (Graph 1).

The Ambulatory represents the territorial reference for all patients with rheumatic diseases in Biella. The rheumatologic diseases affect 10% of Italian population (5.5 million inhabitants) and are in first place among the chronic degenerative diseases. The frequency of rheumatologic diseases in Italy to first place osteoarthritis (73%) followed by extra-articular rheumatism (13%), arthritis (spondyloarthritis, AR, gout) is 6%, the connective diseases 0.6 %, while the prevalence of Paget’s disease is of 0.5-1.5% of patients depending on the different series (1-4).

The Rheumatology Outpatient presents a records of case studies of 4000 patients resident in the territory of Biella and province. We found 20% of the patients with disease’s Paget, representing 0.5% of the patients that pertain to the clinic of rheumatology. Among the rheumatic diseases 657 patients suffering from osteomatabolic diseases [osteoporosis (OP), hyperparathyroidism, Paget’s disease, algodystrophy, aseptic osteonecrosis, osteonecrosis of the jaw (ONJ)] and represent 16% of the casistica; 2.3% of 657 patients is suffering from Paget’s disease.

Our record data consists of 20 patients with Paget’s disease, mean age of 71.46 years, ranging from 60 years to 84 years and the male: female ratio with a slight predominance of females, is 7:8 in Biella. If we analyze the prevalence of Paget’s disease in the Biella’s population of the same age, we find that they are affected 3.3% of those over 60 years.

Of 20 patients as many as 15 were suffering from Paget’s disease with polyostotic disease and only 5 had just a single pagetic location with monostotic localization.

Patients with monostotic localization M:F ratio was 1:4, while the 15 patients in the polyostotic localization M:F ratio was 7:8.

Going on to analyze different sites of pagetic localization see like 14 of 20 patients showed pagetic localization to the bone of the pelvis; 5 to location sacroiliac joint; 4 had localization of 1/3 proximal right humerus.

The involvement of the skull was found in 4 patients, whereas localization in the vertebrae was detected in 7 patients. All patients reported a pain at the site of pagetic localization (Table 1).

Paget’s disease and genetic analysis

19 of the 20 patients were performed the search of the SQSTM1 gene mutation that was found in only two patients, female, both suffering from monostotic Paget, both presented as the only pagetic location the pelvic bone.
Of the two patients (numbers 9 and 10) (Table 1) who had this genetic mutation has been proposed to extend the survey to immediate family members to evaluate possible gene combinations among patients in the area of Biella (same mutation in the population) and possible presence of the same mutation among the immediate families (genetic transmission).

Of these two patients the number 9 was resident in Biella but of Sardinian origin and had the mutation M404V ES8; the number 10 showed, however, the mutation P387L ES7 and had Venetian origin. No patient of Biella origin had the mutation in the studio.

Our study allows to identify two cases of familial aggregation of Paget's disease, the patient number 4 reported having a brother, he suffering from Paget's disease, who suffered also from Parkinson's disease and moreover one cousin also affected by Paget's disease. It was not possible to carry out the investigation on the genetic brother of the lady because he's resident in another region, but the lady who is the cousin turned out to be negative for the presence of the SQSTM1 mutation (Graph 2).

The series included two other first cousins affected by Paget's disease, the number 7 was a female and the number 15 that was a male, both turned out negative for the mutation of the SQSTM1 gene (Graph 3).

The patient number 9 had two daughters, one of 54 years old which suffers from skin psoriasis and the other 50 years old that suffers from multiple sclerosis. The SQSTM1 gene mutation M404V ES8, identical to that found in the mother was present only in the daughter suffer-
ing of multiple sclerosis, which had two other children for whom the genetic investigation is still ongoing. The patient number 10 had only one son, 51 years old, negative for the mutation of the $SQSTM1$ gene (Table 1).
Paget's disease and quality of life

All patients with Paget's disease were investigated for the classification of disease using generic questionnaires that would compile independently at each visit, with questions about the quality of life (HAQ: Health Assessment Questionnaire) and the perception of the degree of pain by patients themselves (VAS: Visual Analogue Scale), as well as assessed by a clinical point of view, also using blood tests and instrumental, and if in active phase of the disease, directed towards the bisphosphonate therapy.

15 of the 20 patients showed elevated levels of total Alkaline Phosphatase (ALP) (Table 2), and were in the active phase of the disease during the first outpatient evaluation, in two cases of poliostotic paget, levels of alkaline phosphatase were significantly higher than normal, up to 40 times too; in majority of cases (8:15) there was an increase of 5 times the normal values; in two other cases an increase of 7-9 times the normal values.

Some patients had alkaline phosphatase increased by 1.5 times the normal values and there were both monostotic Paget location. All patients had normal serum calcium or lower limits but still normal levels of parathyroid hormone in the rule, all patients were receiving vitamin D supplementation weekly.

The evaluation of the quality of life of patients with disease activity was investigated by administration of HAQ, which includes 20 questions related to activities of daily living into eight different categories: washing and dressing, arising, eating, walking, hygiene, objects reach, grasp and other activities. Each question has 4 responses that identify the degree of difficulty in performing the action in question. The sum of the scores divided by 8 is the final score HAQ which includes a score greater than 2 a severe degree of disability, a score between 1 and 2 defines a moderate degree of physical disability, a score greater than 1 indicates a mild degree of physical disability, and a score varies from a minimum of 0 to a maximum of 3. A score greater than 1 indicates a mild degree of physical disability, a score between 1 and 2 defines a moderate degree of physical disability, and a score greater than 2 a severe degree of disability.

At each visit was also asked to provide a quantitative assessment of the intensity of the pain using a visual analogue scale (VAS). The VAS is a linear scale, the visual representation of the amplitude of pain which is shown as a line of 10 cm where the left end is given a value of 0 representing absence of pain, at the right is shown the value of 100 that means specific worst pain imaginable.

The patient must check the appropriate box, the point corresponding to the degree of pain experienced.

The answer is given by measuring the distance in millimeters from the left to cross and indicating the numeric value; it is very useful, especially for assessing pain at specific times or related to ongoing pain, rather than the memory of a previous experience.

In our study, we detected a discrepancy between functional limitation required, in the performance of the most common activities in daily life, and Paget's disease in the active phase, and we realized as Paget's disease does not interfere directly with the activities of daily life, in fact, only in three cases the patients reported clearly limits in the performance of daily activities, but it is likely to conditions beyond Paget.

It is also clear that it is rather the perception of pain intensity the determining factor of Paget's disease, the 15 patients in the active phase of the disease, seven of 15 reported a discomfort directly with the activities of daily life, in fact, only in three cases the patients reported clearly limits in the performance of daily activities, but it is likely to conditions beyond Paget.

Comorbidity and Paget's disease

In the study much attention has been given to the anamnesis and the analysis of comorbidities to Paget's disease. 14 of 20 patients had hypertension in four cases was also associated with angina pectoris and in two cases in previous episodes of myocardial infarction (MI) in a framework of ischemic heart disease-hypertensive. Only in two cases, it was possible to document episodes of transient ischemic attacks (TIA).

Table 2 - Comorbidities in study population.

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AMI (Acute Myocardial Infarction); TIA (Transient Ischemic Attacks); ID (Insulin Dependent); NID (Non Insulin Dependent); OA (Osteoarthritis).
In three cases out of 20 was reported a previous cancer: 1 case of skin cancer, 1 breast cancer and a man with prostate cancer. As part of a framework of plurimetabolic disease three patients were also suffering from Diabetes Mellitus type 2 non-insulin dependent (NID) and all turned out also hypertension. 5 of the 20 patients reported fractures and one patient had a fracture of the pagetic bone (Table 3).

**Paget’s disease and scintigraphy**

All patients underwent bone scintigraphy with Total Body $^{99}$Tc for identification of sites affected and the intensity of osteometabolic, followed radiographic examination or Tc (5). All patients showed an intense uptake to the scintigraphic examination in areas affected by the pagetic disease. After adequate intake of calcium and vitamin D in the weeks prior to therapy, 15 patients, who presented in the active disease, were subjected to treatment with intravenous zoledronic acid.

After 5 days post-infusion a first evaluation of follow-up was carried out through telephone contact to evaluate the eventual presence of the flu-like syndrome post-infusion, which often accompanies the first infusion of zoledronate. Subsequent follow-up inspections, included clinical assessment with collection HAQ and VAS and symptom classification and analysis of blood tests (serum calcium, phosphorus, total alkaline phosphatase and parathyroid hormone) at one month, six months and one year, after the first infusion, and then every six months for better monitoring of the osteometabolic changes, in relation to the pain reported by patients and can thus assess the possibility of a re-infusion of zoledronic acid.

All patients have had a good response to the treatment with zoledronic acid obtained already at 6 months, the normalization of alkaline phosphatase in 90% of cases and reduction in 30% of cases with ALP values greater than 1000 g/dl (Figures 1-8).

In 12 cases the pagetic location is associated with pain mainly characterized by coxalgia, sacroiliitis, and headache.

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**Table 3 - Study population: parameters of Paget’s disease activity.**

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<td>355</td>
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<td>4,7</td>
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<td>4,6</td>
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<td>P (2,7-4,5 mg/dl)</td>
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<td>2,97</td>
<td>3,79</td>
<td>2,64</td>
<td>2,6</td>
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ALP tot (Alkaline Phosphatase total); Ca (calcemia); P (phosphataemia); PTH (Parathyroid Hormone); HAQ (Health Assessment Questionnaire); VAS (Visual Analogue Scale).

Figure 1 - M.P. male 75 yrs. Before (A) and after (B) zoledronate therapy.
L. Longato

**Figure 2** - M.P. male 75 yrs. X-ray of the pelvis: sacroiliac pagetic site.

**Figure 3** - M.P. male 75 yrs. X-ray of the right shoulder.

**Figure 4** - M.E. female 75 yrs. Total body scintigraphy before (A) and after 1 year (B) of treatment.

**Figure 5** - M.E. female 75 yrs. X-ray of the pelvis: dense sclerosis of right hemipelvis with osteolytic lesion.

**Figure 6** - M.E. female 75 yrs. Total body scintigraphy after four years of treatment: no uptake in sites previously involved. Complete remission.

**Figure 5** - M.E. female 75 yrs. X-ray of the pelvis: sacroiliac pagetic site.

**Figure 6** - M.E. female 75 yrs. Total body scintigraphy after four years of treatment: no uptake in sites previously involved. Complete remission.
with full resolution after only 3 months of infusion therapy. In only two cases the pain characterized by sacroiliitis, despite the normalization of the ALP values, persisted after treatment and only the second infusion was achieved remission of pain. It was not necessary to perform a second infusion for 86% of cases, even in two years after the first administration for persistent normalization of ALP values and the absence of pain. Only for two cases it was necessary a second infusion after one year from the first; to the persistence of pain despite the ALP values were maintained in the normal range. In these two cases was the bone scintigraphy in addition to symptoms in detect the real need for a second infusion therapy (Figures 9-12). There were no adverse side effect during the infusion.

Flu-like syndrome and hyperparathyroidism

Despite therapy with calcium and vitamin D in 53% of cases the patients reported the appearance of flu-like syndrome
within 2-3 days after infusion, which did not improve even with taking paracetamol 3g/die.

There was mild hyperparathyroidism in 46% of cases 6 months after infusion, which was then normalized by the daily intake of calcium and vitamin D (Vit D). In 7 cases out of 15 a year later it was found hyperparathyroidism II, despite the normalization of ALP and the daily intake of calcium and Vit D.

Discussion

The Paget’s disease in the series of the Biella Rheumatology Outpatient, is a representative sample of the population that statistically should be affected by the disease. Indeed the territory of Biella has a higher prevalence in rural areas, mountains and rice paddies, many farms are and common practice is to have pets as well as livestock and poultry; and almost all patients with Paget’s disease reported since their childhood a close contact with dogs and other animals such as sheep, goats, cattle, etc.

It is important to emphasize that migration flows from the post World War II brought about the arrival in the territory of a predominantly textile manufacturing workers, from the Veneto and Sardinia as well as from southern Italy, that influenced at least from the point of view of genetic characteristics to affect the epidemiology of Paget’s disease in Biella territory (6-9).

The search for mutations in the $SQSTM1$ gene, on the other hand, was found in two patients with Paget’s disease that were of Sardinian origin and Venetian respectively. No native from Biella area presented this type of mutation, and although the series is limited, and does not lend itself to analysis of population, it is curious that there are two cases of families with relatives suffering from Paget, but none of these were positive for the mutation of the $SQSTM1$ gene (Graphs 2 and 3). These data suggest the importance of genetic studies of mutations that certainly as assumption of the disease and the need for research in these families Pagetic aggregation, the presence of other possible genetic mutations, that are likely to determine the transmissibility of the disease, as it has been possible to document for the $SQSTM1$ mutation (10-15).

From a clinical point of view most of the patients presented, according to the frequency localization, in the bones of the pelvis (65%), the spine (35%), skull (20%), sacroiliac joints (25%); between other localizations less typical stands out the commitment to load in the proximal region of the humerus (20%) (16, 17).

In 75% of cases were detected poliostotic Paget’s disease and in 25% of cases, or in other words, only 5 patients were monostotic. Of these, three patients had a single location in the bones of the pelvis, 1 patient had unique location as the skull and 1 patient borne by the third right proximal humerus.

Just the two patients who had a positive mutation of $SQSTM1$ gene were suffering from monostotic Paget’s disease and values that express alkaline phosphatase activity osteometabolic disease were moderately elevated (500 IU/l) (Tables 1 and 2).

Among patients with a poliostotic Paget’s disease, we found the highest increase in alkaline phosphatase and these, were also associated with greater pain detected by the VAS, while there appears to be no correlation with the normal activities of daily living, investigated through the questionnaire HAQ.

Patients with active disease showed increments of the values of alkaline phosphatase and increased uptake of the scintigraphic examination in the areas within the bone pain, were subjected to intravenous therapy with zoledronate and evaluated in subsequent follow-up.

Our research shows that treatment with zoledronate in Paget’s disease, in the active phase of disease, is associated with rapid and sustained remission of both indices of bone remodeling that symptoms related to it. Although well tolerated, has common side effects such as flu-like syn-
drome rather important post-infusion characterized by fever, shaking chills, and fatigue common arthromyalgia, unresponsive to full doses of paracetamol, but of short duration, a maximum of three days, followed by well-being (18). There are frequent cases of hyperparathyroidism II, resulting in transient hypocalcaemia occurring despite the higher doses, compared to the daily needs of calcium and vitamin D. The power and long-term persistence of zoledronate is highlighted by a progressive reduction in ALP levels even after 6 months and indirectly by hyperparathyroidism II as result of transitional hypocalcaemias that can be detected even after 1 year of the first infusion, indirect index of the continuous activity of the drug in the pagetic bone. Despite the therapeutic indications described on zoledronate technical form required infusions annual repeated, we decide taking into account power antiresorptive drug, to evaluate the real need for reinfusion on the basis of clinical data and blood chemistry and instrumental that indicated an exacerbation of clinical symptoms. This specific action, let us to consider the possibility of a second infusion of zoledronic acid, only in cases in which it is observed persistence of pain borne by the districts affected by Paget's disease, or elevated levels of total alkaline phosphatase, or bone and yet the persistence of increased uptake in scintigraphic examination. Evaluating the real need to repeat intravenous therapy, the efficacy of inhibiting the activity osteo-metabolic pagetic bone and remission time between the phases of reactivation. Bone scintigraphy proved to be an effective valuable tool for evaluation of disease activity in the presence of pain in subjects with values of total alkaline phosphatase in the normal range. This review highlights areas of increased uptake and intense osteometabolic persist after infusion therapy suggesting the real need for re-treatment intravenous bisphosphonates (19). The potency of the drug was higher than assumed and does not require a subsequent annual infusion, as is shown in the technical form, while demonstrating the importance of re-evaluate patients even after 1 year to monitor their levels of calcium, phosphate and PTH and continuing integrating daily calcium and Vit D. Further clinical studies should be conducted on a wider coverage to confirm these preliminary data and appropriate considerations should be made for the indication of osteoporosis patients treated with intravenous zoledronate, in order to better assess the need for subsequent infusions at annual intervals, according to chart technique (20). Decisive is the supportive therapy with calcium and vitamin D in the long term, to reduce as far as possible the onset of transient hypocalcaemia and consequent increases in blood levels of parathyroid hormone.
Acknowledgements. The author gratefully acknowledges the University of Florence and especially Prof. Brandi and her team for giving me the opportunity to seek unconditional genetic mutations in Pagetic patients related to Rheumatology Clinic.

References