

Tenosynovial complications identify TTR cardiac amyloidosis among patients with hypertrophic cardiomyopathy phenotype

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Abstract. Cappelli F, Zampieri M, Fumagalli C, Nardi G, Del Monaco G, Matucci Cerinic M, Allinovi M, Taborchi G, Martone R, Gabriele M, Ungar A, Moggi Pignone A, Marchionni N, Di Mario C, Olivetto I, Peretto F (Careggi University Hospital, Florence; Azienda Ospedaliera Careggi, Florence; Careggi University Hospital, Florence; University of Florence, Florence; and Careggi University Hospital, Florence, Italy). Tenosynovial complications identify TTR cardiac amyloidosis among patients with hypertrophic cardiomyopathy phenotype (Original). *J Intern Med* 2021; **289**: 831–839. <https://doi.org/10.1111/joim.13200>

Recent evidence suggests that carpal tunnel syndrome (CTS) and brachial biceps tendon rupture (BBTR) represent red flags for ATTR cardiac amyloidosis (ATTR-CA). The prevalence of upper limb tenosynovial complications in conditions entering differential diagnosis with CA, such as HCM or Anderson–Fabry disease (AFD), and hence their predictive accuracy in this setting, still remains unresolved. Objective: To investigate the prevalence of CTS and BBTR in a consecutive cohort of ATTR-CA patients, compared with patients with HCM or AFD and with individuals without cardiac disease history. Participants: Consecutive patients

with a diagnosis of ATTR-CA, HCM and AFD were evaluated. A control group of consecutive patients was recruited among subjects hospitalized for noncardiac reasons and no cardiac disease history. The presence of BBTR, CTS or prior surgery related to these conditions was ascertained. Results: 342 patients were prospectively enrolled, including 168 ATTR-CA (141 ATTRwt, 27 ATTRm), 81 with HCM/AFD ($N = 72$ and 9 , respectively) and 93 controls. CTS was present in 75% ATTR-CA patients, compared with 13% and 10% of HCM/AFD and controls ($P = 0.0001$ for both comparisons). Bilateral CTS was present in 60% of ATTR-CA patients, while it was rare (2%) in the other groups. BBTR was present in 44% of ATTR-CA patients, 8% of controls and 1% in HCM/AFD. Conclusions: CTS and BBTR are fivefold more prevalent in ATTR-CA patients compared with cardiac patients with other hypertrophic phenotypes. Positive predictive accuracy for ATTR-CA is highest when involvement is bilateral. Upper limb assessment of patients with HCM phenotypes is a simple and effective way to raise suspicion of ATTR-CA.

Keywords: brachial biceps tendon rupture, cardiac amyloidosis, carpal tunnel syndrome, popeye sign, transthyretin.

Introduction

Transthyretin (TTR) amyloidosis is a cause of heart failure (HF) accounting for approximately 15% of diagnoses in older patients presenting with preserved ejection fraction (HFpEF) [1, 2]. TTR cardiac amyloidosis (CA) is caused by amyloid deposits in the heart that can be due to a mutated

(ATTRm) or a wild-type form of transthyretin (ATTRwt) [3]. In recent years, total body scintigraphy with phosphonates, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-DPD), ^{99m}Tc-hydroxymethylene diphosphonate (Tc-HMDP) and ^{99m}Tc-pyrophosphate (Tc-PYP), has gained an important role in the diagnosis of ATTR-CA greatly simplifying the diagnostic algorithm

[4-10]. As a result, the perceived incidence and prevalence of ATTR-CA, especially of the ATTRwt subtype, has rapidly increased, surpassing other forms of CA.

Recent evidence has consistently shown the frequent involvement of tenosynovial structures in ATTR amyloidosis. A history of carpal tunnel syndrome (CTS) or previous carpal tunnel surgery is common in ATTR-CA patients [11, 12] and may precede cardiac involvement by several years. Furthermore, in patients with ATTRwt-CA, amyloid infiltration of the brachial biceps tenosynovium may weaken the tendon structure causing rupture that can be spontaneous or subsequent to slight efforts [13, 14]. In the cohort reported by Geller *et al.*, brachial biceps tendon rupture (BBTR) was reported in one third of ATTRwt patients and in only 2.5% of patients with other causes of HF. Therefore, a combined assessment of upper limb tenosynovial signs might have a role in the evaluation of patients with a hypertrophic cardiomyopathy phenotype, often hiding ATTR-CA. To date, however, the prevalence of these signs in the upper limbs, in conditions entering differential diagnosis with cardiac amyloidosis such as HCM or Anderson-Fabry disease (AFD), and hence their predictive accuracy in this setting, still remains unknown. Consequently, we aimed to investigate the prevalence of CTS and BBTR in a consecutive cohort of ATTR-CA patients, compared with a cohort of patients with HCM or AFD and with an age-matched cohort of individuals without history of cardiac disease.

Patients and methods

Patient selection

Study participants were enrolled between 1 January and 31 December 2019. All signed a written informed consent, and study protocol was approved by local ethical committee reference number 16115.

ATTR-CA

Consecutive patients with a diagnosis of ATTR-CA evaluated at the Tuscan Amyloid Referral Centre (Careggi University Hospital, Florence, Italy) were prospectively enrolled. Diagnosis of CA was performed by demonstration of ATTR deposit at endomyocardial biopsy analysed with immunohistochemistry or immune electron microscopy, or according to the noninvasive diagnostic algorithm suggested by Gillmore *et al.*, that is by a Perugini grade 2-3 cardiac uptake in a bone-seeking tracer

radionuclide scintigraphy, in the absence of detectable serum and/or urine monoclonal protein, normal free light chain ratio and with echocardiogram or MRI suggestive of amyloidosis [6]. A further differentiation between ATTRm and ATTRwt was performed by the presence/absence of related gene mutation at ATTR gene sequencing.

HCM and anderson-fabry disease

Consecutive patients affected by HCM or AFD were prospectively enrolled in the same time period in the cardiomyopathy unit of the Careggi University Hospital, Florence, Italy. Criteria for diagnosis followed established protocols according to existing guidelines [15, 16].

Controls

A control group of consecutive patients recruited among subjects hospitalized in the IV Internal Medicine Division, Careggi University Hospital, Florence, Italy, for noncardiac reasons and with no medical history of cardiac disease was recruited and screened for BBTR and CTS. By study design, controls were of comparable age to the ATTR-CA group (due to the fact that tenosynovial complications tend to be age-related), whereas HCM/AFD patients were typically younger (Table 1).

Assessment of upper limb tenosynovial complications: CTS and BBTR

The presence of prior CTS release surgery was specifically ascertained. Symptoms potentially associated with CTS were investigated, and symptomatic patients were referred for neurological assessment to confirm the diagnosis. Brachial biceps clinical examination was performed in all subjects, and the presence of tendon rupture was defined by the presence of the Popeye sign (Figure 1), that is descent of the muscle in the middle part of the arm, which becomes more obvious with contraction. In patients with evidence of tendon rupture, precipitating circumstances such as trauma or an intense physical effort were investigated. Due to the high suspicion for cardiac amyloidosis, all patients with bilateral CTS or BBTR were screened by investigations specific for ATTR-CA, including HMDP bone tracer scintigraphy, even though they came for unrelated reasons.

Statistical analysis

Data were analysed with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean $\pm$ standard deviation. The

Table 1. General presenting features and tenosynovial complications in the 342 study subjects

	Hypertrophic Phenotype (n = 249)			P-value ATTR-CA vs HCM/AFD	P-value ATTR-CA vs Control
	ATTR-CA (n = 168)	HCM/AFD (n = 81)	Control group (n = 93)		
Age years	77.9 ± 8.1	56.9 ± 11.6	76.8 ± 10.3	0.0001	0.349
Gender (male)	151 (90%)	43 (53%)	57 (58%)	0.0001	0.0001
BSA, m ²	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.1	0.477	0.823
NYHA class			N/A		N/A
I	44	40	N/A	Overall	N/A
II	93	32	N/A	0.005	N/A
III	30	9	N/A		N/A
IV	1	0	N/A		N/A
ASP, mmhg	125.4 ± 15.8	125 ± 16.8	N/A	0.827	N/A
ADP, mmhg	72.6 ± 9.7	75.9 ± 10.4	N/A	0.018	N/A
Atrial fibrillation, yes	76 (45%)	15 (19%)	N/A	0.0001	N/A
Pacemaker, yes	20 (12%)	8 (10%)	N/A	0.665	N/A
IVS, mm	17.6 ± 2.9	18.3 ± 5.1	N/A	0.210	N/A
PW, mm	16.2 ± 2.7	10.6 ± 2.2	N/A	0.0001	N/A
LVEDV, ml	95.7 ± 28.5	101.8 ± 31.3	N/A	0.164	N/A
LVESV, ml	41.1 ± 20.6	37.1 ± 14.4	N/A	0.0001	N/A
EF, %	54.5 ± 9.9	63.9 ± 7.9	N/A	0.0001	N/A
E, cm/s	85.7 ± 20.1	72.1 ± 20.7	N/A	0.0001	N/A
A, cm/s	59.1 ± 29.6	67.9 ± 23.5	N/A	0.0520	N/A
E/A	1.8 ± 1.1	1.1 ± 0.6	N/A	0.0001	N/A
E/E'	17.3 ± 6.2	10.1 ± 5.6	N/A	0.0001	N/A
Tenosynovial complications					
Any upper limb involv. yes/no	138 (82%)	11 (14%)	15 (16%)	0.0001	0.0001
CTS, yes/no	122 (73%)	11 (13%)	9 (10%)	0.0001	0.0001
Bilateral CTS, yes/no	100 (60%)	2 (2%)	2 (2%)	0.0001	0.0001
Year since CTS diagnosis	8.1 ± 5.1	2.3 ± 1.9	7.8 ± 6.1	0.0120	0.873
BBTR, yes/no	74 (44%)	1 (1%)	8 (8%)	0.0001	0.0001
Bilateral BBTR, yes/no	26 (15%)	0	1 (1%)	0.0001	0.0001
CTS&BBTR, yes/no	58 (34%)	1 (1%)	2 (2%)	0.0001	0.0001

ADP, arterial diastolic pressure; AFD, Anderson–Fabry disease; ASP, arterial systolic pressure; ATTR-CA, ATTR cardiac amyloidosis; BBTR, brachial biceps tendon rupture.; BSA, body surface area; CTS, carpal tunnel syndrome; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVEDV, left ventricular diastolic volume; LVESV, left ventricular systolic volume; NYHA, New York Heart Association; PW, LV posterior wall.

proportions of categorical variables were compared using a chi-square analysis or Fisher's exact test as appropriate. Normally distributed continuous variables were compared using the Student t-test for independent samples. For non-normally distributed variables, the Mann–Whitney U-test was used. When more than two groups were analysed, a

comparison with ANOVA followed by Scheffe's post hoc analysis was employed. To evaluate the odds ratio of CTS and BBTR in discriminating between subjects affected and not affected by ATTR-CA, a logistic binomial regression analysis corrected by age and gender was performed. To avoid co-linearity, three models were tested, Model 1 with any



Figure 1 Brachial biceps tendon rupture with descent of the muscle in the middle part of the arm (black arrows), which becomes more obvious with contraction (Popeye sign). Photo published with patient consent.

upper limb tenosynovial involvement (CTS, BBTR or both); Model 2 with CTS and BBTR, irrespectively if mono or bilateral; and Model 3 testing the presence of bilateral CTS and BBTR. A P -value < 0.05 (2-sided) was considered significant. For any upper limb tenosynovial complications, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in ATTR-CA diagnosis were tested both in whole population and in hypertrophic phenotype subgroup (ATTR-CA, HCM/AFD).

Results

General patient features

Between 1 January 2019 and 31 December 2019, 342 patients were prospectively enrolled, including 168 with ATTR-CA (141 ATTRwt, 27 ATTRm: 16 Ile68Leu, 6 Val122Ile, 5 other private mutations), 81 with HCM/AFD ($N = 72$ and 9, respectively) and 93 age-matched subjects without history of cardiac disease (Table 1). Patients with ATTR-CA were older, more often male and with more advanced HF symptoms assessed by NYHA class, compared with HCM/AFD (Table 2). ATTR-CA patients more often had concentric left ventricular (LV) wall thickening with a slight reduction in LV EF and more pronounced diastolic dysfunction compared with HCM/AFD (Table 1). No difference was observed in kidney function between ATTR-CA and HCM/AFD (1.1 ± 0.4 vs 1.1 ± 0.6 $P = 0.539$). No differences were evidenced in LV chamber dimensions, LVEF, and E/E' in patient with CTS or any upper limb tenosynovial involvement compared with patient without CTS or upper limb tenosynovial involvement.

Prevalence of upper limb tenosynovial complications

Overall, evidence of prior or active tenosynovial complications including CTS and/or BBTR was

detected in 164 of the 342 (48%) study subjects, with strikingly skewed distribution. Of the 168 ATTR-CA patients, 138 had at least one of the two features (82%), and 58 had both (34%). By comparison, these proportions in the HCM/AFD and control group were 14% and 16% vs 1% and 2%, respectively (Table 1). Thus, the prevalence of any upper limb tenosynovial complications was between four and six times higher in the ATTR-CA group compared with each of the other two groups. Among ATTR-CA patients, prevalence of CTS and BBTR differed according to different aetiologies, as shown in Figure 2. Both any CTS and bilateral CTS were similarly distributed between ATTR-CA aetiologies, while BBTR was more prevalent in ATTRwt-CA (Figure 2).

Sensitivity, specificity and predictive value of tenosynovial complications with regard to a diagnosis of ATTR-CA (both in the whole study cohort and in the specific context of a hypertrophic phenotype) are shown in Table 2. For any tenosynovial complication, positive and negative predictive value in the overall study group including controls was 84% and 83%, respectively, with an accuracy of 84%. In the ATTR-CA + HCM/AFD population, these values were 93% and 70% with an accuracy of 83% (Table 2). Of note, history of bilateral CTS or bilateral BBTR had 98% and 100% positive predictive value, respectively.

Independent diagnostic value

On a multivariable logistic regression analysis including age and gender, the presence of one or more tenosynovial complications was associated with a 24-fold increase in likelihood of ATTR-CA in the whole study group (OR 24.6, 95% CI 12.6–47.9, $P = 0.0001$; Table 3). In the specific context of a hypertrophic phenotype, the increase was 40-fold (Table 3).

Table 2. Sensitivity, specificity and predictive value of tenosynovial complications with regard to a final diagnosis of ATTR-CA

	Any upper limb involv.	CTS	Bilateral CTS	BBTR	Bilateral BBTR
Whole population (ATTR-CA + HCM/AFD + controls; <i>n</i> = 342)					
True positive	138	122	100	74	26
True negative	148	154	170	165	173
False positive	26	20	4	9	1
False negative	30	46	68	94	142
Sensitivity	82%	73%	60%	44%	16%
Specificity	85%	89%	98%	95%	99%
Positive predic. value	84%	86%	96%	89%	96%
Negative predic. value	83%	77%	72%	64%	55%
Accuracy	84%	81%	79%	70%	58%
Hypertrophic phenotype (ATTR-CA + HCM/AFD <i>n</i> = 249)					
True positive	138	122	100	74	26
True negative	70	70	79	80	81
False positive	11	11	2	1	0
False negative	30	46	68	94	142
Sensitivity	82%	73%	60%	44%	16%
Specificity	86%	86%	98%	99%	100%
Positive predic. value	93%	92%	98%	99%	100%
Negative predic. value	70%	60%	54%	46%	36%
Accuracy	84%	77%	72%	62%	43%

AFD, Anderson–Fabry disease; ATTR-CA, ATTR cardiac amyloidosis; BBTR, brachial biceps tendon rupture; CTS, carpal tunnel syndrome; HCM, hypertrophic cardiomyopathy.

In the whole population, the presence of bilateral CTS was associated with an approximately 90-fold increase in the independent likelihood of ATTR-CA (OR 90.1, 95% CI 22.8–355.6, $P = 0.0001$), while the increase for BBTR was equal to 4.7 (OR 4.7, 95% CI 1.9–11.6, $P = 0.0001$). In the specific context of hypertrophic phenotype, the presence of bilateral CTS increased the independent likelihood of a ATTR-CA diagnosis of about 25 times (OR 25.1, 95% CI 2.1–296.2, $P = 0.0001$), while a BBTR increased it by 10 times (OR 10.6, 95% CI 1.1–106.1, $P = 0.0001$).

CTS

CTS was present in 75% of patients with ATTR-CA when compared to 13% and 10% in HCM/AFD and controls ($P = 0.0001$ for both comparisons; Table 1). Bilateral CTS was present in 60% of ATTR-CA patients, while it was rare (2%) in the other groups. Moreover, CTS became clinically evident approximately 8 years before enrolment in

ATTR-CA patients and controls, but only 2 years before in HCM/AFD.

BBTR

Brachial biceps tendon rupture was present in 44% of ATTR-CA patients, in 8% of controls and in 1% (1 out of 81) in HCM/AFD. Bilateral BBTR was reported in 15% of ATTR-CA patients, in 1 control subject and in none of the HCM/AFD group. In 1 ATTR-CA patient, in 1 HCM patient and in 2 control subjects, BBTR was related to a major trauma. In all other patients, BBTR occurred spontaneously or after slight effort. In ATTR-CA, 20% of the patients with BBTR were not aware of ligament lesion, which was diagnosed as a spontaneous rupture during physical examination.

Discussion

The present study systematically assessed the prevalence of upper limb tenosynovial involvement

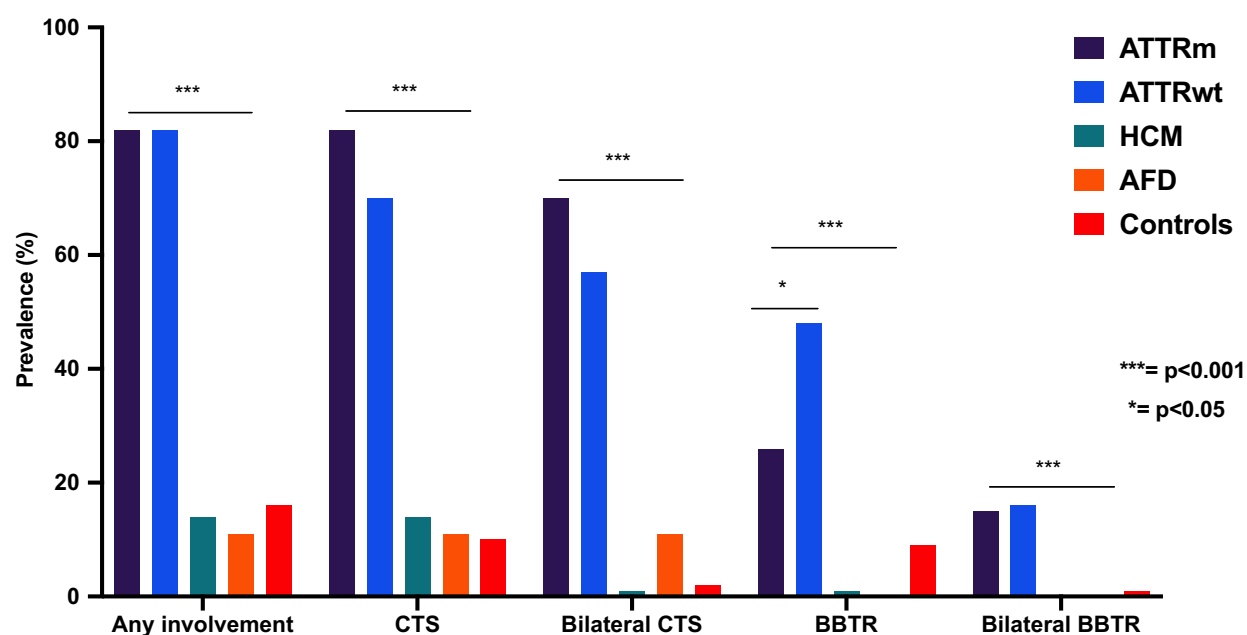


Figure 2 Prevalence of upper limb tenosynovial complications according to aetiology and in controls. CTS, carpal tunnel syndrome; BBTR, brachial biceps tendon rupture; ATTR, transthyretin amyloidosis; HCM, hypertrophic cardiomyopathy; AFD, Anderson-Fabry disease.

Table 3. Logistic regression analysis endpoint ATTR-CA in clinical characteristics in whole population

	B	Wald	OR (95% CI)	P=
Whole population (ATTR-CA + HCM/AFD + controls; n = 342)				
Age	0.07	20.90	1.07 (1.04–1.11)	0.0001
Gender (female)	−1.64	15.84	0.19 (0.08–0.43)	0.0001
Any upper limb involve.	3.22	88.40	24.57 (12.60–47.89)	0.0001
Hypertrophic phenotype (ATTR-CA + HCM/AFD n = 249)				
Age	0.19	36.88	1.21 (1.13–1.28)	0.0001
Gender (female)	−2.02	8.50	0.13 (0.03–0.51)	0.004
Any upper limb involve.	3.70	28.17	40.76 (10.36–160.24)	0.0001

ATTR-CA, ATTR cardiac amyloidosis; AFD, Anderson-Fabry disease; HCM, hypertrophic cardiomyopathy.

(CTS and BBTR) in consecutive ATTR-CA patients compared with a cohort of hypertrophic phenocopies (HCM/AFD) and age-matched subjects without a history of cardiac disease. Our data show that ATTR-CA patients presented evidence of at least one upper limb tenosynovial involvement in 82% of cases, a > 5-fold increase in prevalence compared with the 14% and 16% prevalence in the HCM/AFD and control group. CTS was the more common sign, affecting almost three quarters of ATTR-CA patients, as opposed to only 13% of

HCM/AFD patients and 10% of controls. The fact that bilateral involvement occurred in 60% of the ATTR-CA group, but was rare (2%) in the other two groups, should be highlighted. Likewise, the prevalence of BBTR was 44% in patients with ATTR-CA compared with 1% in HCM/AFD and 8% in the control group. The slight discrepancy in frequency between these last two groups is nonsignificant and possibly reflects the older age of the latter. Consistently, bilateral rupture affected 15% of ATTR-CA patients but only one subject in the

control group and none among HCM/AFD patients. We observed a similar occurrence of CTS in ATTRwt and ATTRm, in agreement with the report by Ausdem Siepen *et al.* [16]. With regard to absolute prevalence, the 75% value found in our patients represents the highest reported so far (20–51%)[17,18]. The discrepancy is largely due to two facts: a) we have actively and prospectively looked for carpal tunnel in our population, while prior reports are based on prior surgical release of CTS (i.e. not including patients who were symptomatic but did not undergo an operation); and b) our cohort is skewed towards a cardiac phenotype, more often associated with CTS. We acknowledge the fact that the cardiological setting may have influenced CTS prevalence when compared to ATTR cohorts in other setting. Nevertheless, the present study was specifically intended to provide values relevant to clinical practice in cardiology clinics.

In the ATTRwt group, the frequency of BBTR (48%) was slightly greater but in an order of magnitude similar to that previously reported [14]. In ATTR-CA subpopulations, the prevalence of BBTR was significantly lower in ATTRm compared with the ATTRwt group (Figure 2).

On logistic regression analysis, the presence of any upper limb complication (CTS, BBTR or both) was associated with a 24-fold independent increase in likelihood of ATTR-CA in the overall population. This was increased 41-fold when the analysis was limited to cardiac patients with a hypertrophic phenotype. Such increase can be explained by the fact that HCM/AFD patients were on average considerably younger than ATTR-CA individuals, reflecting real-world clinical practice. Consequent to such striking imbalance, upper limb tenosynovial involvement was highly accurate in the identification of ATTR-CA, with 93% positive and 70% negative predictive value. In the presence of bilateral CTS, the positive predictive value increased to 96% and 98% in the whole population and in the hypertrophic phenotype subgroup, respectively. Bilateral BBTR was a much less common occurrence, but had a 100% positive predictive value for ATTR-CA in patients with a hypertrophic phenotype. The association of bilateral tenosynovial involvement with ATTR-CA appears to be so strong that it should prompt a revisitation even of well-established diagnoses of HCM, in order to exclude superimposition of amyloidosis in older patients.

Both CTS and BBTR represent key diagnostic red flags supporting clinicians in pursuing a suspicion of ATTR-CA. A brief medical history and simple physical examination can provide decisive diagnostic clues needed to suspect ATTR-CA and refer to second-level imaging evaluation such as cardiac MRI and bone tracer scintigraphy [19]. As recently demonstrated by Maurizi *et al.* in patients referred to cardiomyopathy centres with an initial diagnosis of HCM, CA was the most common unrecognized underlying disorder with a 9% overall prevalence that increased with age (ranging from 1% at ages 40–49 years to 26% above 80 years) [20]. A prompt diagnosis is particularly important now that several pharmacological treatments based on precursor protein stabilization or circulating TTR level lowering may impact on ATTR progression [21–24]. Since these therapies act by preventing deposition of new fibrils but cannot remove the amyloid already present in the heart, it is imperatively an early start before the establishment of a severe irreversible cardiac impairment.

The physiopathologic mechanism leading to tenosynovial involvement in ATTR has not been completely elucidated. Recently, an *in vivo* study demonstrated that proteolysis of the TTR tetramer by plasmin may provide a critical concentration of both truncated and full-length TTR protomers required for nucleation of ATTR fibrils [25]. Once nucleation occurs, the seeding effect could accelerate elongation of amyloid fibres with lower concentration of ATTR monomers [25,26]. As mechanical forces seem to play an important role in TTR fibrillogenesis, structures such as tendons and the myocardium may represent common targets for amyloid deposition due to their permanent exposure to mechanical stimulation [25]. Notably, these complications do not develop in parallel. CTS becomes clinically evident on average 10 years prior to cardiac involvement in ATTR. This delay could be explained with the smaller amount of amyloid deposition required to cause clinical complications in fine tendons and ligaments, as compared to the bulkier cardiac mass. However, as shown by Sperry *et al.*, in a series of 8 patients with ATTR diagnosed analyzing tissues removed during CTS surgery, only one subject showed a simultaneous heart involvement by Tc-PYP scintigraphy [11]. Therefore, the temporal discrepancy of cardiac as opposed to tenosynovial involvement remains unexplained and should be the aim of further studies.

In conclusion, upper limb tenosynovial complications including CTS and BBTR are 5-fold more prevalent in ATTR-CA patients compared with cardiac patients with other hypertrophic phenotypes. Positive predictive accuracy for ATTR-CA is highest when involvement is bilateral. Upper limb assessment of patients with HCM phenotypes is a simple and effective way to raise suspicion of ATTR-CA, allowing appropriate referral to second-line examinations.

Limits

Age and gender of the three groups of individuals enrolled in our study are incompletely matched due to well-known differences in the age range at presentation in ATTR-CA vs HCM/AFD, and different gender composition. ATTR-CA patients are older and with greater male predominance compared with HCM/AFD. Nevertheless, after age and gender adjustment, upper limb tenosynovial involvement retained an impressive association with ATTR-CA. We acknowledge that patients with CTS may have been preferentially referred to our clinic reflecting the increasing awareness of its role as a red flag for ATTR-CA. A broader spectrum of tenosynovial manifestations in ATTR might include other features, such as lumbar spinal stenosis, which was not assessed in our study.

Funding

The present study was supported by an Investigator-Initiated Research from Pfizer Srl. Pfizer Srl. had no role in the study design, data analysis and result interpretation of the present study.

Conflict of interest

None declared.

Author contribution

Cappelli Francesco: Conceptualization (lead); Data curation (lead); Funding acquisition (lead); Methodology (lead); Writing-original draft (lead). **Mattia Zampieri:** Conceptualization (equal); Data curation (equal); Writing-original draft (equal). **Carlo Fumagalli:** Data curation (equal); Formal analysis (equal); Investigation (equal). **Giulia Nardi:** Data curation (equal); Investigation (equal); Project administration (equal). **Guido Del Monaco:** Data curation (equal); Formal analysis (equal); Investigation (equal); Software (equal). **Marco**

Matucci-Cerinic: Supervision (equal); Visualization (equal); Writing-review & editing (equal). **Marco Allinovi:** Project administration (equal); Supervision (equal); Writing-review & editing (equal). **Giulia Taborchi:** Conceptualization (equal); Formal analysis (equal); Project administration (equal). **Raffaele Martone:** Data curation (equal); Formal analysis (equal); Investigation (equal). **Martina Gabriele:** Conceptualization (equal); Data curation (equal); Methodology (equal); Project administration (equal). **Andrea Ungar:** Supervision (equal); Visualization (equal); Writing-review & editing (equal). **Alberto Moggi Pignone:** Validation (equal); Visualization (equal); Writing-review & editing (equal). **Carlo Di Mario:** Supervision (equal); Visualization (equal); Writing-original draft (equal). **Iacopo Olivetto:** Conceptualization (equal); Methodology (equal); Writing-original draft (equal). **Federico Perfetto:** Conceptualization (equal); Data curation (equal); Methodology (equal); Writing-original draft (equal).

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